U s . Food and Drug Administration

Science Board

Meeting

May 19, 1998

9:50 a.m.

Doubletree Hotel

Plaza Room II

1750 Rockville Pike

Rockville, Maryland

Members of the Board in attendance:

David M. Kipnis, M.D., Chair

Robert Langer, Sc.D.

Leslie Z. Benet, Ph.D.

Charles Sanders, Ph.D.

Gilbert A. Leveille, Ph.D.

Richard B. Setlow, Ph.D.

Pedro Cuatrecasas, M.D.

Marion Nestle, Ph.D., M.P.H.

Invited Guest:

Bernard Liebler, M.S., HIMA

FDA participants:

Elkan R. Blout, Ph.D., Senior Advisor for Science, FDA

Michael A. Friedman, M.D. , Lead Deputy Commissioner, FDA

Bernard A. Schwetz, D.V.M., Ph.D., Interim Chief Scientist, FDA

Susan K. Meadows, M.S., Executive Secretary, FDA Science Board

Elizabeth D. Jacobson, Ph.D., Deputy Director for Science, CDRH

Donald E. Marlowe, Director, Office of Science and Technology, CDRH

Kathryn C. Zoon, Ph.D., Director, CBER

Neil D. Goldman, Ph.D., Associate Director for Research, CBER

Susan Homire, D.V.M., Office of Science.

Neil Wilcox, D.V.M., M.P.H., Office of Science

Donna Mentch, Office of Science

Brenda Gomez, Office of Science

Agenda

PRO CE E D I NG S

DR . KIPNIS: Elkan. Dr. Blout, would you care to make the introductions?

DR . BLOUT : We have a new member -- at least we did have. Oh, she's getting coffee.

I'm very pleased to welcome Dr. Marion Nestle as the newest appointment to the Science Board. As most of you know, she's an outstanding worker in the field of nutrition. She's now Professor and Chair of the Department of Nutrition at NYU, and she comes to NYU from the other side of the country, where she took her degrees at Berkeley.

We're very happy to have her here. She'll provide scientific expertise and guidance for us in issues regarding nutrition and also in part represent consumer interests on these issues.

I could tell you all her accomplishments . I won't do that, but she's a potentially very good member of this Board, and we welcome her.

DR . KIPNIS: Thank you very much, Dr.

Blout.

We have, as I indicated, a fairly busy schedule today. I'd like to welcome all of the members who are here, many of the FDA personnel, and those of the public. The public will have an opportunity to comment in this afternoon's session.

Several of the reports are status reports to the committee, of committees/ subcommittees we either formed or we requested attention to a specific topic. There is, of considerable interest to many of the Science committee, a presentation this morning on "Public Awareness of FDA Science". Dr. Michael Friedman, the lead Deputy Commissioner, will be here at 10:15 to participate in that presentation.

Most members of the Board and its subcommittees are seriously concerned about the fiscal constraints, both by budgetary decisions in Congress as well as from other sources that have restrained or restricted the development of science within the FDA, a development which

most of us consider essential for it to in essence perform its regulatory function in an appropriate manner.

I think the members of the Board who are here are Dr. Benet, Dr. Setlow, Dr. Leveille, Dr. Marion Nestle who has just been introduced, Dr. Pedro Cuatrecasas, Dr. Bob Langer. I don't know if Dr. Sanders is here yet this morning. Was he scheduled to attend?

VOICE: Yes.

DR. KIPNIS: I wonder if the other members of the FDA would care to introduce themselves?

DR. BLOUT: Maybe David, we should mention that a Board member, Bob Langer, has just received an outstanding award, the Lemuelson prize. It's only been awarded three or four times, and we are pleased that you received this award, and we hope it will allow you to continue to serve on the Science Board.

(Laughter)

DR. KIPNIS: Congratulations.

DR. LANGER: Thank you very much.

DR. KIPNIS: Bern, do you want to introduce yourself, then we'll just go around.

DR. SCHWETZ: I'm Bernard Schwetz, the Interim Chief Scientist of the FDA, working in the Office of Science, and also the Director of the National Center for Toxicological Research.

MS. MEADOWS: I'm Susan Meadows, I'm the Executive Secretary to the Science Board.

DR. WILCOX: Neil Wilcox, Office of Science.

MR. LIEBLER: Bernie Liebler from the Health Industry Manufacturers Association, here to report on the Biomaterials Forum.

DR. JACOBSON: I'm Liz Jacobson, from the Center for Devices and Radiological Health.

DR. MARLOWE: I'm Don Marlowe, Center for Devices and Radiological Health.

DR. KIPNIS: Thank you. There will be various other members of the FDA sitting at the table, depending upon the presentations to be made.

Susan, do you have some housekeeping remarks to make for us?

MS. MEADOWS: We have just a few things. One is, I would remind all of you, particularly the audience, to please use the microphones when speaking so that we can get you into the official record.

Please note that there's no break listed this morning, nor a break listed this afternoon. Please help yourselves, board members, to the refreshments as you need them, and take breaks as you need them.

We are going to move through the schedule fairly quickly. A couple items for the Science Board members. You have a mailing package inserted into your notebook. Should you want us to mail your materials to you, please insert them into the mailer, and we will take care of that for you. Just leave them at the table after you're finished.

We have had a change in the way that we reimburse our expenses, and I would plea to you, we would like to reimburse you for your expenses. It will be done with the new system, and we unfortunately have to have you do direct

deposit forms. So please send those in as soon as possible so that we can take care of this for you.

DR. BLOUT: I will tell you, I've had experience the last month, and it works. Things have arrived.

DR. KIPNIS: We'll start this mornings's proceedings with the Status Reports.

One was the Subcommittee on Toxicology, which was chaired by Dr. Richard Setlow, a Member of the Board. The committee was formed because very early in its deliberations, it recognized the increasing importance of toxicology and the advent of newer elements of science, which broadened the horizons of toxicology and how best to in essence accommodate those rapid changes in the FDA.

Dr. Setlow.

Subsequent to Dr. Setlow's presentation, Dr. Wilcox, from the Office of Science, will also make some comments.

DR. SETLOW: The Science Board, Subcommittee on Toxicology met actually last September. We had a long meeting. We got together with a facilitator, and over the next few months arrived at a vision and a mission.

Neil Wilcox, of the Office of Science, boiled the five general things down into three, and I'll present them, at the moment. You'll find copies of these in your black notebooks, for those that don't wish to remember or to copy.

In any event, the vision is we're committed of course to protecting public health through improved toxicological testing methods, and our mission is to coordinate a collaborative effort between public and private sectors to develop better methods for doing toxicological testing.

I could spend a lot of time on these, but I can give handouts if anyone really needs them.

There were three goals that were summarized for me by Neil Wilcox with approval

by me . The first is to identify areas of toxicity testing, and there are four objectives:

Develop a comprehensive list of testing areas, prioritize areas of toxicity testing for the purpose of continued study by the Science subcommittee;

Select specific standardized testing methods within priority areas; and from these methods in Objective 3,

Conduct a retrospective review to compare preclinical and clinical regulatory data to determine the extent to which safety and efficacy were adequately protected and predicted.

So that's Goal A. Under each of these objectives there's an action plan; but those of you sitting in the rear couldn't read the fine print in the action plan if I really showed it, but it exists, and 1'11 just give you an example at the end.

so each of these goals has objectives, each objective has action plans. So that's

Goal A. There are only going to be three goals, so bear with me.

Goal B is to foster and facilitate the development of more predictive toxicological models through a coordinated effort that targets high priority endpoints. And the objectives, 1, 2, 3, 4, 5 are really to identify testing areas, identifying new and emerging alternative testing methods, establish criteria -- it doesn't do any good to identify unless you have some way of measuring what YOU wish to measure. Identify potential contributions from basic science, suggesting paradigm shifts, and identify programs where mechanism-based research, et cetera, are developed.

So these all have objectives. And the last goal with its objectives, is to encourage acceptance and integration of new testing methods into regulatory and industry decision-making . Obviously if we have great new things, they're not going to be of any use unless they're going to be used, which means unless

they're going to be accepted by both sides of the problem.

so these objectives are to support the acceptance and integration. We have to develop a process that encourages industry to submit data for new, more predictive tests. They have to be validated and they have to be accepted internationally, not just nationally, not just in Washington, D.C. or in Rockville. We have to promote the development of new methods, facilitate continuing education, encourage international harmonization, and then regularly review product safety evaluation for the purpose of identifying and prioritizing effective approaches.

[Overhead]

So that was Goal C, and I'm going to end by just flashing UP -- You can't read 't ' under each Goal, for example, in Goal B, there are a number of action plans. A whole set. And we have copies if anyone wishes, but these are how we're going to approach these goals.

I will end with just one example from

the literature of what's going on.

[Overhead]

Again, you can't read it except for the headline. The National Toxicology Program is really pushing transgenic animals. This isn't only in the National Toxicology Program, but it has to do with the FDA.

So in the Office of Testing and Research, they're trying to stimulate people to develop and invest in some new approaches and supply new insight into risk assessment, and that's Joe Contrera. Just as an example of all sides of the system trying to develop quicker, better, easier predictive methods.

So this is where we are. If we're to go further, we have to have obviously more meetings. We've had a lot of input from committee members by Email, but in order to synthesize that into something, we really have to sit around the table and decide how we're going to do that; and I know, speakin9 for Neil Wilcox, he would say "naturally, we need more resources to accomplish that final goal. "

We're halfway there, but we need something else.

Thanks .

DR . KIPNIS: Thank you, Dr. Setlow.

Dr. Wilcox, did you have any additional comments that you wanted to make?

DR . WILCOX: No prepared documents, Dr. Kipnis, but we would ask the Science Board if you have any questions or comments on the objectives that Dr. Setlow has just presented.

DR . KIPNIS: Are their comments by the Board?

Dr. Leveille.

DR . LEVEILLE: Not a comment, a question. What's the next step with these in terms of implementation?

DR . WILCOX: The next step is a difficult one. As Dr. Setlow alluded to, we'll convene the committee, probably late summer, early fall, and explore options for how do we move forward in what is clearly a long range plan that is resource-intens ive, quite frankly.

The genesis for this endeavor really

started a couple years ago with the recommendations from this Board for the agency to review its approach to toxicology. And in doing so, that in and of itself has many dimensions, and it requires looking at what types of data currently exist that we can mine, if you will, to see how well we've done in our preclinical studies compared to our clinical studies; where have we done well and where are there data gaps where we need better methods to generate data on endpoints that are more specific for what we're looking for.

So this then will lead to recommending research -- or, what I like to refer to as directed research to develop methods that target specific endpoints that we don't currently target.

So this really involves looking at what we currently do and then -- an eye toward the future in trying to stimulate research in the private sector to come up with a better method. So in an environment when we are trying to live day-to-day and put out fires,

it's hard to come up with such a comprehensive program for the future, but that's indeed what we want to do. And hopefully the Subcommittee on Toxicology will act as a consortium to bring resources together.

DR. KIPNIS: Dr. Setlow?

DR. SETLOW: I should say that the industrial members of this subcommittee are also working hard, and they're trying to establish a toxicological database of results from the industry point of view that would be available.

DR. KIPNIS: I recall that there had been previous discussions about that, and the concerns of confidentiality were also raised at that point. Have they been addressed in some of your deliberations?

DR. SETLOW: We have not yet as a committee, but I know that the industrial members are concerned with this and are trying to devise a way of doing this.

DR. WILCOX: There is, if I may add -- there's an international effort going on that's

been organized by Dr. Kathy Stitzel from Procter & Gamble. And in a meeting last fall, which was a very promising meeting, representatives from industry and academia and various government agencies from around the world gathered, and there was a great deal of enthusiasm and optimism about being able to go into industry and actually use their data without giving away confidential, proprietary information.

There is at least one model that we're currently looking at in Europe; it's called the Lhasa model, not to be confused with a lhasa apso -- but this model, where they actually go in and they use the data to develop a predictive modeling system without really knowing what the total chemical moiety from which it came, so it doesn't give away trade secrets.

So it's doable, and there's interest if we can get by the attorneys.

DR. KIPNIS: Dr. Schwetz, did you have some comments?

DR. SCHWETZ: Thank you, Dr. Kipnis. There is a point that I wanted to raise that is relevant to the recommendations that the Science Board made that led to this discussion and review within the agency of these new toxicology approaches.

Those of us within the field of toxicology have been saying -- a lot of us have been saying for years that we should replace some of the empirical tests that we use with mechanism-based tests. That was before the mechanism-based tests were close by, and there was support and enthusiasm for that idea.

Now the transgenic models represent mechanism-based test models that are here, and in the evaluation and validation stage, and I see something going on between government, industry and academia, the people who are all interested in the development and use of these methods that is contrary to what you recommended. And now that the methods are here, there's a building resistance to use them.

Dr. Setlow mentioned the NTP review. I was on the Board of Scientific Counselors for that specific review of the transgenic program that NIEHS and the NTP has; and within that Board of Scientific Counselors review there was a pretty strong sentiment to just throw all this out because it isn't going to work, in reference to transgenic animal models for predicting carcinogenesis.

There are a number of reasons why I think there is reluctance to change now in all of these sectors, to use transgenic models in lieu of the two-year bioassay for detecting carcinogenic activity; but it kind of stands in the way of what you were recommending earlier, that the FDA use the best scientific methods that we can. Because now there is a tendency to be reluctant to do that.

DR. KIPNIS: May I ask, is the reluctance to the science, or is it to scientific considerations or other elements involved in this?

DR. SCHWETZ: I think to some extent

it's just the reluctance of change, and also that the test methods are not fully validated yet. There's a fear that we don't know how to use these new methods; and it's either going to prolong the length of time it takes to make a decision, or we're going to use transgenic models and then turn around and say "Well, we're not sure how to interpret the data, so you have to do two year studies anyhow. "

DR. KIPNIS: Dr. Leveille.

DR. LEVEILLE: Well, that really gets to the point of my original question; the, in food area as contrasted to the drug area, the issue becomes even more complex when you think about international harmonization of regulations and so on.

The constraint against using new technology is really a regulatory one; the model we've evolved in this country is the establishment of a template against which everything has to match exactly. So a new method coming along requires a change in a template which doesn't occur readily; and

that's really the dilemma.

So what the committee is I think working on is to get increased flexibility into the system, and at the same time find a way to quickly get international harmonization and acceptance of new approaches. And that's critical, but the ability to change the system is a crucial factor, and that's why I ask how quickly we're going to move to implementation, because currently the system does not allow that flexibility.

DR. KIPNIS: Dr. Cuatrecasas?

DR. CUATRECASAS: I would think, at least in my experience, that the reluctance to move forward more rapidly with transgenic animals in toxicology is based on the science. There's certainly no reluctance to proceed with respect to biological activity, with respect to using these as models of disease, novel models which previously didn't exist.

There are so many uncertainties related to, and so much ambiguity as to what value a transgenic may have in a toxicological

study that people are reluctant to use these, and I think correctly, quite yet. I think we have to be more patient.

I am much more encouraged in what I have heard, and I want to congratulate and support the committee in what it's doing. As I look at what's happening in companies and at the FDA with respect to toxicological testing, I see tremendous progress over the last ten, even five years. There's no comparison.

The discussion and the level of involvement of mechanistic toxicology is incomparably further along than it was before. There are many, many approaches to mechanistic other than using transgenic animals, as we know; in cellular biology, molecular biology, and in so many other approaches I see that the industrial toxicologist is being encouraged and have found a receptive audience.

I've experienced some really very exciting discussions, and resolutions of problems based on scientific concepts and methodologies which I think are fairly modern.

So I'm not sure the subcommittee's efforts are responsible; but I think that in part certainly symbolically that we should give encouragement, and in that indirect and intangible way I think that you might have an effect.

DR. WILCOX: Thank you, Dr. Cuatrecasas. What you just stated so eloquently is a very important factor in this international attempt to look at the new technology and what we're doing, and the mere fact that we have this committee, and that we are willing to look forward and bring people together from all the different stakeholders, that in and of itself has been a tremendous impetus and note of encouragement to the international scientific community.

And there are efforts going on internationally in a tremendous display of cooperation and eagerness to work together toward the many dimensions in this area of toxicological testing and new methods.

So it's been exciting, and the message

that we sent has been very positively received.

DR. KIPNIS: I noted the term, 'international activities.' I think that's to be encouraged. The customer base which the FDA deals with is increasingly internationalized. And indeed, you don't know who's what and what's who anymore in terms of interactions; so it's critically important that international actions are encouraged. And there's no one monopoly on scientific knowledge or creativity, and we ought to take advantage of it all.

But the other is another point; and that is, anytime any new methodology is introduced, validation is an important element to it. One of the concerns I have is, who is going to do the validation, because that does take time and it does take money, and it takes effort. And things have to be validated.

Is that potentially a cooperative venture in which there will be multi-institutional -- when I say institution now, I'm talking about government, industry and

academia involved in certain validation efforts. If there is no validation, we may be back to the same questions a year or two years from now.

DR. SETLOW: Well, the committee consists of academia, industry, and government; and I think they're working together. And that's the only way that we're going to get an answer. Each of these members has input via Email to a big circle of collaborators, and they all have suggestions coming in. So I think this is going to be the direction, to validate.

DR. WILCOX: As a matter of fact, there is a new entity that has been formed as a standing committee; and the impetus for it was a mandate that came out of the 1993 NIH revitalization act; and it's called the Interagency Coordinating Committee for the Validation of Alternative Methods. It has now become a standing committee, and has created a center that is run by an external contracted group that is housed within the National

Institute for Environmental Health Sciences and the National Toxicology Program jointly.

The purpose of this group, called ICCVAM, is to review and assist in the validation of new methods. And ultimately, once it has determined that a method is validated for its intended purpose, to then bring it to the regulatory agencies and suggest that this method exists, to demonstrate what it has been validated for, and then it would be up to the individual agencies to incorporate these new methods into the regulatory paradigm.

As a matter of fact, this afternoon 1'11 be speaking at a congressional briefing where there has been a consortium of industry members that have come together; Proctor & Gamble , Colgate and three or four others, where they are sponsoring a bill to help fund this new ICCVAM committee that is made up of 15 different federal agencies.

So there is a tremendous amount going on in the arena of validation.

DR . KIPNIS: Why don't we go on, in

order to stay close to our schedule, to the next report, by Mr. Bernard Liebler, who is the Director of Technology and Regulatory Affairs of the Health Industry Manufacturers Association, for an update on the Biomaterials Forum.

MR. LIEBLER: Thank you. In your package is a one-sheet report entitled: Biomaterials Forum, Progress Report and Recommendation.

The recommendation is very short. It says: We recommend that we place the project to develop a Biomaterials Forum indefinitely on hold.

The original intent of the forum was to develop a means for improved communication, particularly for the FDA, to deal with their customers, the device companies in our case. And also academia and anyone else that had an interest in the biomaterials area. It was mostly spurred by the biomaterials shortage that occurred I guess about five years ago now, and in many ways still continues.

What's happened in the interim is, FDA -- particularly CDRH, has undergone a reengineering program, and revived the product development protocol, which was in the original device amendments, which allows for increased communication with the agency on exactly how a product will be developed and tested from the very beginning.

Also, the new Modernization Act allows for, and requires meetings on clinical studies and again on the data that will be required very early in the approval process. And the feedback I've been getting from other people; I was talking to one member or I got an Email from one member of our subcommittee, Peter Johnson who runs the Tissue Initiative out at University of Pittsburgh, who was saying that he was at a meeting last week that again demonstrated the improved communication.

We think that the attention that was brought by the forum work plus all these other activities has led to the kind of communication we wanted to see. So that pursuing the forum

in a formal manner which would be developing a web site and probably expending a good deal of time and money is probably not useful at this point. It's an idea that still remains viable if it's needed in the future, and the Science Board can always revive it.

1'11 be glad to answer any questions.

DR. KIPNIS: Are there any other comments?

DR. BLOUT: Bernie, what do you see about -- what new materials, improved materials are being developed?

MR. LIEBLER: That's a hard one to even begin to address. Traditionally, materials for devices have not been developed for devices. And considering the market sizes, it's hard to believe that traditional materials are going to be developed, traditional type materials.

I think that you really need to talk to someone like Peter Johnson, who really has a good understanding of tissue engineer. Because I think tissue engineering and that kind of

bioengineered hybrid material is where things are going to have to go. A better stainless steel is certainly not going to be developed, just as an example, for a medical device.

It may be for an automobile. Those people buy it by the carload and ton; we buy it by the cup full and the gram. It's not worth anybody's money.

DR. MARLOWE: Mr. Chairman, I think you have one of the world experts sitting at this table on your panel that can speak to the evolution of materials. And I think Bob Langer would agree with me that the evolution is going to be away from traditional materials, as the Science Advisor just asked, and towards materials that are more actively engaged in the process of body rebuilding or organ replacement. We're going to see a paradigm shift over the next ten years in materials; materials ten years hence won't look anything like the materials that we're using today.

DR. LANGER: I agree with what both of you are saying. I think from a scientific

standpoint there's no question that what you're saying is right. I think the impediment to creating new materials is often legal issues in terms of lawsuits. That's been the biggest single problem discouraging innovation.

I think when I lectured here a couple of years ago at one of the meetings, one of the points -- and I think Bernie could probably give statistics on this -- is that what you've seen is a number of these small medical device companies who are very innovative, you see the percentages decreasing in the U.S. and increasing other places.

I think one of the -- and you also see a decrease in innovation, and in large companies like Dupont, the classic example is, Dupont spent more money defending themselves on lawsuits that they never lost than they ever made on selling one of their materials to a company that was making an artificial jaw.

So I think it's more the laws that are creating the impediment. Medically I think what you're saying is exactly right, because

the bulk -- the tissue engineering in many other areas, the need to create materials that can be tailor made to improve and save human lives is absolutely there. But I think what we also see, a legal problem in this country, and I think that makes it hard.

DR. KIPNIS: By the way, there are two other individuals from the FDA here; Dr. Elizabeth Jacobson, who is the Deputy Director for Science, and Mr. Don Marlowe, Director of Office of Science and Technology. Any comments?

DR. JACOBSON: I just wanted to add one comment, and that that has to do with sort of another shift in the regulatory handling of materials that's been allowed by the new law. And that is that as a result of the new law, we're allowed to recognize consensus standards in the premarket review process. And I think that's going to have another helpful push to increase communications, and will allow easier harmonization.

The emphasis on the use of standards

is going to do things like encourage the MOU that we already have with NIST and NIH to develop standard reference materials. And that ought to help, maybe it will even help with the legal arena where everyone in the world is agreeing on standards related to biomaterials.

DR. KIPNIS: Any other comments?

If not, thank you for all the participants, and we'll go on to the next item on our agenda, which is: Public Awareness of FDA Science. Two of the individuals who will comment about that are Dr. Michael Friedman, who is the Lead Deputy Commissioner of the FDA, and Dr. Elkan Blout, who is the senior Science Adviser at the FDA.

Dr. Friedman?

DR. FRIEDMAN: Thank you. I'd like to spend a couple of minutes talking about a variety of issues. The title of this is not complete or completely accurate, but it does convey at least some of the thoughts that I wanted to share with you.

There are really three or four issues

that I wanted to touch on; and I'll ask Elkan to please interpolate as I deal with each one of these. The first is that this Board has been very consistent in its urging us to consider in its support of the recruitment and appointment of the Chief Scientist; and we are all very committed to doing that.

The announcement for the availability of such a position is going out. You have been asked in the past, and you will continue to be asked for your suggestions about who such an individual would be. We very much would appreciate that.

Elkan I think has some remarks about how he sees this process developing; but this is not a mere figurehead; this is an important representation of agency commitment and a much more precise focus in terms of both internally and externally leveraging what's the very skeleton and framework of our agency in that science.

Elkan, what would you add?

DR. BLOUT: I consider this one of the

most important positions the FDA has created. We would like your suggestions of people who could be candidates for this position. David Kipnis is going to chair the search committee; the search committee is being formed now. And we're beginning to find -- we have found a few people who would be appropriate.

My thought is, the chief scientist must be an internationally-recogni zed scientist, and we start from there. He could come from academia, from industry or from government , but he must be internationally recognized as a symbol of science.

Secondly, Dr. Friedman is modest. He has made available funds through the budgeting process to make this position attractive to the person who is chosen. And we hope this will be a really outstanding position.

DR . FRIEDMAN: I should clarify that those funds are for discretionary use and not salary funds, because we can't make it as attractive as we would like.

But Elkan is quite right; the sort of

candidate that we're looking for, he or she must be a very distinguished scientist, must be capable, must be articulate, must want to create and share a vision of clinical and laboratory science at the Food and Drug Administration, and that's a very important responsibility, and we're going to do everything we can to move that search along.

That' s number one. Number two is, a very satisfactory exercise that scientists within the agency have been working on, which both laboratory and clinical scientists from all divisions within the agency have been meeting under the leadership of Bern, to answer a number of questions that I've posed to them.

I have been proceeding on a couple of hypotheses, but realized that I hadn't had those hypotheses formally vetted. One hypothesis was that everybody would agree that science is critical to the agency and it should be no surprise to YOU that these scientists reaffirmed that and said yes, that was their understanding as well, and their vision as

well.

The second was that the needs for good scientific input broadly ranged across the entire agency, that there was no one component of the agency that needed science more or less than other components within the agency. And that can be challenged. That was my thinking, but I asked them to please challenge that and tell me if they agreed.

And again perhaps not surprisingly but in a very satisfying way, the scientists all agreed that all components, all the divisions within the agency required -- not deserved, that's the wrong word -- required good science in order to do their job. That was very helpful to me.

Because I told them that if they had come back to me and said that there is one area that needs this acutely now, that we would all work together to try and address it. They could not identify that but did say that broadly and in a number of areas across the agency, there were important needs that should

be addressed. And I very much appreciated their input.

What they also did was to begin to craft a priority list of agenda items, scientific issues that they thought were most important to the agency. Not just for today, but where we want to be in two, three and five years. And I appreciated that very much.

That's a process that's ongoing but it represents the sort of forward planning that I think is exactly appropriate and essential for us to complete.

Let me link that with the third point -- and 1'11 just ask whether you want to add anything to that at this time?

DR. BLOUT: No, not at this time.

DR. FRIEDMAN: Okay. It was a very helpful exercise; it shows how unselfish and collegial the scientists can be in caring about the interests of science broadly across the agency. These were not parochial interests, these were very broad public health interests.

The third thing really is how those

interests can be integrated into a larger package. And this is the point where I am making a pitch to this group, to everyone who's listening, as I have been to virtually every constituency with which we deal.

One of the segments of the FDA Modernization Act of last year, in Section 406, and I am told it is Section 406(b) although for all the world, it looks like 406(f) ; but none the less, the agency is instructed to do the following: To consult with appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups in the regulated industry to develop and publish in the Federal Register a plan bringing the Secretary into compliance with each of the obligations of the Secretary under this Act, and "this act" refers to the Food, Drug and Cosmetic Act -- it is a modification of the Food, Drug and Cosmetic Act.

This exercise to me is an extremely important exercise, because what it does is it

means that we are instructed to go to each of our constituencies and to say to them: What gaps currently exist between what is called for and what we are doing? Please help us prioritize that, please help us identify ways to address that, and in order for us to then propose to the administration, to the Secretary and to our congressional committees ways in which we wish to deal with those things, to be part of that process.

Now the reason I think that's such an important activity is that it mirrors exactly some of the things that many of you have told me privately, and that you've said publicly, about the needs to address scientific activities within the agency. Since I see science not as a separate line item, not as something that sits, in sort of splendid isolation, but as really being integral to everything that we do, I think this group, this committee and others can help have input to those considerations.

This first report, which must be a

yearly annual report, will be published by November 21st of 1998, in the Federal Register. We're instructed to do that and we take this, as we take all of our FDA modernization responsibilities very, very seriously. That leaves us relatively little time for this first iteration.

There are three broad areas that we have identified as being important. We are going to all of our constituencies, all the stakeholders who have a vested interest, and asking them to please comment on but also to add and to re-prioritize interests; so by saying to you three things that we are focusing on today that's not to suggest at all that that's the limit or that's even the order of the ones that will be picked. But it is to say that we have to do part of this, which is to begin to create this formal agenda.

We've tried to pick things where we see important gaps that exist between statutory requirements in our performance and things which will have important public health

benefit, and those two things must go hand in hand.

The three areas that we've identified so far as being very important are: Adverse event recognition reporting, modification, management . I don't think anybody could argue that that's an important area. It is broadly true for the entire agency. I'm not talking about drugs, I'm talking about requirements for devices, but also for foods, for cosmetics, for a number of other areas.

We're not only talking about a better system for evaluation and management; this is I think a perfect example where science and research skills are incredibly necessary. Here we're talking about epidemiologic and statistical, but also clinical skills.

So I think this should be a topic of interest.

The second is the broad area of how we assure the quality and safety of products, inspection and compliance activities, where there are important gaps that exist between our

statutory requirements and our ability to perform; and we are talking again to a wide variety of organizations.

I should just reiterate here, we have not reached out to all the organizations; but I'm doing this -- as meetings come along, I and other people are making this case to the public, and we will be doing so in a more formal way. This is sort of a welcoming of people to please come to us, even on bid, and say we'd like to offer you our proposals, we'd like to share with you our division of what this should be.

That second area is an important one. The third is in the general area of premarket review activities. As you all recognize, for human drugs and biologics, the Prescription Drug User Fee program has been spectacularly successful, but there are other important product areas where the agency is not meeting its statutory deadlines. We're doing beautifully with human drugs and biological; we do not have such a good record in some other

areas, and I fear our performance in those areas will actually get worse as budgetary constraints weigh heavily upon us.

There are important benefits for the public that will be delayed if we can't move as quickly and with as much care as we would like. Again, it should be obvious to you that there are opportunities for science; laboratory investigation and non-laboratory investigation, that are relevant to these areas.

I don't mean this to be a comprehensive list; I'm giving you just a shorthand version of three areas that we think, we believe are important that we believe broadly, the community, the lay community, industry, governmental organizations, that others will also feel are very important. But the list is much longer than this, and our concerns are to prioritize those things that we think are most critical or most accessible during this next fiscal year to begins to craft ways in which we address those issues.

And let me just restate: I'm not

suggesting that we simply throw money at things, although resources will be an important part of this. What we're asking for also is ideas of ways in which we can discharge these responsibilities in innovative, novel ways that may save resources or may do a better job.

So this is not a commitment to do things in the same old way; it is a commitment to meet what the public expectations are, and that's our ongoing goal.

How can you all be helpful in this? Well, I think you can imagine a number of ways in which you could be helpful. As these discussions go further, as we're able to flesh out better what we are, what we are see are our most near term goals. You all can have input to that, you can help change that agenda, you can suggest resources or ways to address what will be necessary; you can give us ideas of how to do our job better.

I think this provides a public means for discussion, and that' s very important. This is a public discussion which is called for

by the Act, and we want to conform fully to what the Act requires.

Let me stop there and answer any questions, if I may.

DR. KIPNIS: Any comments by members of the Board?

DR. CUATRECASAS: Could you elaborate a little more on the second issue that you discussed?

DR. FRIEDMAN: You mean inspections?

DR. CUATRECASAS: Yes.

DR. FRIEDMAN: There are a variety of industries where we have -- where there are statutory guidelines for how often a facility will be inspected and we're not in full compliance with that? And I think that we want to figure out how to address that.

1'11 give you some other examples. We've entered into a number of mutual recognition activities with foreign governments for facilities that are there. Living up to those obligations will be difficult in real time. We think that international activities

are very important, but we're trying to say, rather than taking a decade to meet certain expectations, can we bring that down to a more reasonable time frame and are there other countries that we aren't even able to engage in activities with now who we could think about?

Again, it's not just a matter of drugs and biologics; it's generic drugs, it's devices, it's all sorts of things -- animal products. It's very broad ranging, and I think that what we want to do is look at what are those statutory expectations that have the most public health benefit? Those are the ones we want to focus on first.

The background of this is that I think that the agency has demonstrated that when we get the resources and when we have clear goals, we do a great job. When we don't have the resources or the goals, the expectations are not so clearly articulated, we do a less good job. And we want to try and fix both of those things.

The agency's budget has roughly

doubled between the beginning of the decade and the end of the decade. And our workload has probably gone up five or six or eightfold, depending upon how you look at it; so that even with much greater efficiency, which I give the centers and the management of the agency tremendous credit for increased efficiencies, even with that we're still struggling to meet our obligations; and we just need to recognize that and to engage with the public and with the public's representatives in Congress; what do we want as citizens, how do we want it, and what are we prepared to provide in order to get that?

It's just a very serious, nonemotional, analytic discussion.

DR. CUATRECASAS: Thank you.

DR. FRIEDMAN: Like all of our discussions.

(Laughter)

DR. BLOUT: Thank you, Mike, for that last few words.

I just have two points I'd like to

make to the Science Board. One, this search for a chief scientist is really starting now, and many of us here would like to see it completed within about six months. We want to get somebody on board, the right person. So please send in suggestions as soon as possible, and they can go either to Dr. Kipnis or to me.

Secondly, I want to say a few words about my personal experience. During the slightly more than six years I've served in this position, I've had many positive experiences at FDA. But it would only be fair to say, I've had many frustrations. And the frustrations generally encompass the feeling that people outside the agency don't understand what the agency is trying to do or how they're trying to do it.

I think the awareness of the agency's scientific work within, both in terms of laboratory work in the various centers and its use of science is not appreciated widely in our society. And I would urge us to think how we can convey to the people who make decisions

about the agency, the importance of science.

We should stop talking to ourselves exclusively. We've got to talk to ourselves often. But we should try and talk to other people, to the staffs of congressional committees, to the important people relating to appropriations .

So anybody who has ideas or is willing to participate in this activity, let's go.

DR. FRIEDMAN: Let me give the usual bureaucratic clarification. What Elkan is not suggesting, of course, is lobbying activities that we're asking for from the agency. We're talking about educational activities -- I think he's talking about educational activities, and I want to be very clear about that.

The points to remember are the vast investment that's being made by the pharmaceutical industry by device manufacturers, by food companies, cosmetics, the whole -- veterinary products. We're talking of something getting close to $40 billion a year just in R&D in the United

States, including NIH.

It is inconceivable that that amount of investment won't result in important products in the near and more products in the long-term future. And what we're talking about is having an agency that is prepared to deal scientifically with the breadth and the depth of those products.

And unless we want to go back to a time when things are slowly evaluated, I don't think anybody does, then we must have a system in place that is suitably vigorous and efficient to deal with this vast number of new products that we're going to be facing.

So how do we best do that; and I think science is an important component. Simply educating people about that, simply asking people, what are your expectations for the future, I think is a useful sort of discussion.

DR. KIPNIS: Dr. Leveille?

DR. LEVEILLE: That's certainly true, as you well know, Dr. Friedman, in the food area, in spades. Good or bad, the focus has

really changed by the food safety concerns that have emanated over the past few years. The unfortunate thing is that CFSAN in FDA has had to divert increasingly limited resources to activities other than premarket evaluation; and that has been very seriously damaged. They have not been able to deal with any citizens petitions that have come before them; they have not been able to deal with other premarket submissions that have come before them, in an efficient way. Very different from the drug side, as you well know, and I would hope that would be one of the areas that would get early attention.

DR. FRIEDMAN: I think that's well said; I think there are a variety of nonuser fee areas where those same concerns are true. I recognize and agree with what you're saying, and I think there are important benefits for the public. It's not just the law, we're supposed to be doing things in certain statutory frameworks, time frames; it best serves the public's interest.

We're not satisfied with that; we want to try and address that, too. And we think that, looking at our processes, looking at our resources, these are the things that we want to broadly engage everybody in.

DR. KIPNIS: I'd like to make a few comments relevant to some of the issues that have been raised repetitively by Dr. Friedman as well as Dr. Blout and others, and that is: Consistency of recognition even within the agency that it is science-based. For the four years I've participated in this committee, every single official, well before your administration, has always introduced the comment that it's science-based. Indeed, even the legal personnel have used those terms.

The problem is there's a distinction between hyperbole and substance. And if they really mean what they say their actions ought to be based on.

I would present two things that are argumentative, but nevertheless strike me. One is that science has been used as the base for

the FDA being involved in the critical issue of tobacco. The issue of nicotine addiction is a scientific-based phenomena. Indeed, it was known, but much of that information never released to the public even by industry in this essence.

Also, the epidemiologic data relating smoking with malignancy is well known. So there are scientific bases that legitimize the approach . On the other hand, a major decision was made on biomedical materials based on a political decision without substantive science behind it. The breast implant data is an example of that.

So the consistency of the FDA from its leadership to its most minor participant has to be consistent that we are science-based. Now I've heard that repeatedly said; but part of it is a part of the, I would say celiac axis and hypothalamus other than just the white cortex. Until it is felt deep, it won't be appreciated.

Now that is within the agency; but the other is the public, that expects a great deal

of the FDA, but doesn't realize that its decisions have to be based on the best quantitative data you can secure with respect to what science permits you to secure.

I think, therefore, the issue of educating the public is critically important. But the public also elects representatives; and most of the representatives are public in this sense, as well is their staff. And do they feel that science is important?

I'll give you an example of where I think Congress and its representatives and its staff recognize that scientific-based information, given in a neutral manner without political impact was important. And that did with the sunshine laws, and the legal interpretation constraining the National Academy in terms of its capacity to respond as a neutral source of scientific information.

Within one month, both houses of Congress unanimously passed legislation and it was signed, acknowledging history going back to 1860, where a neutral scientific factual body

should be free to present information but keep the public informed; indeed, membership of the societies informed, and reports.

So that it is an educational event; but I would say even internally, by what I've seen for four years, that has to be an espousal at the highest levels including the legal people who are involved to distinguish between what is a political decision and what's science based.

The other deals with user feels. I must admit, I'm confused as to why industry on one hand expects high quality, rapid decision-making, but in essence is unwilling to acknowledge that user fees basically are personnel sorts -- it's people; it's not the computers that are doing the work. Once you have them, it's the cheapest element. But it's people.

And yet to acknowledge that user fees are a legitimate basis for increasing the quality of science so that you have better people who make the decisions is something I

have a hard time to understand. It seems as if one's talking out of both sides of one's mouth; and I acknowledge that' s a legal issue, that's a political issue; but purely from management, how can you improve the quality of your scientists if you can't also put into it the cost of making the decision. In order to make that decision, you need the quality people as well as the number of people needed to reach those decisions. Those are comments; take them or leave them.

DR . FRIEDMAN: Let me address briefly both those areas. One is that we aspire to be a science based agency, and sometimes as science unfolds we're proven to be correct or we're proven to have not had all the information in making certain decisions.

I think that this body and the public should hold us accountable in a very severe way for how well we use scientific information; and that we recognize that at any moment in time -- as scientists we recognize this -- we have insufficient information to have a full view of

things; and what we're called upon to do is make the best decisions given that moment. Then to be charged with reevaluating that decision forever, as new information comes in.

I hope that's what we've done successfully over the past couple of years, anyway; because I think I've seen a lot of serious commitment to that sort of activity, even in the face of very controversial decisions in virtually all of our product areas; where some community has said we haven't gotten the science right, and other communities have said that we have. And you can think about that for foods, for devices, for drugs, for virtually every area that we've been involved in. And we're prepared for that sort of vigorous scientific discussion and even controversy. That' s number one.

Number two is, I actually think it's not as worthwhile to focus on where resources will come from to do those activities that are necessary for the agency as it is to decide first what needs to be done and then at what

level and with what sort of resources; and then to decide where those resources should come from.

Leaving aside the validity of your argument , David, about -- you know, for a particular area. And that's something that has been discussed, it can be discussed more. I honestly feel that's not as important, because there are a ton of other areas within the agency that don't have user fees and for whom resources for scientific activities are absolutely essential.

So leaving aside that question, because I don't quite agree with your synthesis of it, but that's not important; you're making the case that in order to do good reviews and to manage portfolios properly, you need the proper science. I certainly agree with that. What I would like to do is not to get involved right away and where the resources will come from, because I think that's going to be actually diverting and confusing and contentious .

What I would like to do first is just say: What do we want to do, What is it going to take, and then we will decide how we will pay for it. Otherwise we get short-circuited into -- as you point out, these can be difficult, contentious political and special interest issues. We don't need to go there right yet. We will need to go there, and I'm not avoiding that . I'm prepared to deal with the difficulties of those discussions; that's fine. But let's do that third. Let's first decide what do we want and what is it going to take.

Let me just close my section, if I can, by apologizing; I've got to run to another meeting, and I'm sorry that I won't be able to be here for a lot of the very important presentations and discussions that will take place later. But if people have comments specifically for me, you know how to get ahold of me. I'm not in the witness protection program yet, so --

(Laughter)

-- please feel free to -- Bern or

Elkan or others will convey things to me; you can get to me directly. And I'm sorry, I wish I could stay for the rest of the afternoon. Thank you.

DR. KIPNIS: Thank you very much, Dr. Friedman.

Why don't we go on to the next presentation, by Dr. Leslie Benet, the Subcommittee for CBER Review.

DR. BENET: Let me say something before Mike leaves, because I thought he was going to stay for this part; because we are going to disagree with his premise in terms of what is needed for the agency, and we are going to state more of what our chairman had indicated in terms of, that we are in a crisis situation in CBER, and that the present approach that is going on within the agency, which is reflective of the government funding criteria, is something that requires a committee such as ours that are not employees of the federal government , to make recommendations.

Specifically, the committee feels that

with Senate bill 1305 presented in October 22, 1997, the National Investment Act of 1998, where the bill calls for increased U.S. Government appropriations for basic scientific, medical and preemptive engineering research in federal government institutions, but that the Food and Drug Administration is omitted from this, is a grave error that can lead to a great crisis in health of the population and of the economy.

So this committee is going to make recommendations that will reflect what we believe needs to be there, Mike, but also are going to vigorously make recommendations in terms of funding of the agency relative to this.

DR. FRIEDMAN: I appreciate that, and welcome those comments. I don't see that as inconsistent with what I've said.

My understanding is that you all have had a chance only to review the Center for Biologics. And however passionately you make the case for them, and I think it's deserved --

we have no disagreement about that.

I don't think you can say, without having reviewed the other areas, that the needs in one area are more desperate than in others. Make the case generally that -- if you can; I'm not trying to put words in your mouth -- if you make the case that these are urgent needs, and I not only accept; I welcome those remarks, that this is not at all inconsistent with what I'm saying, but that these are agency-wide issues.

What I look to this Board to do is to help provide the perspective agency-wide. Make the best, most passionate, most convincing case you can, center-by-center as you review it; but recognize, I think, what our scientists have told us internally and what I think is sort of generally accepted folk wisdom; is that the issues in CDRH or the issues in CFSAN or the issues in CDER, CVM, are not fundamentally different than the issues in biologics; and our biologics laboratories are an important national resource. I think they're very

valuable to us. I think they're essential to our operating properly.

Make that case wherever you see it. If you find that you don't see it for one of our centers, fine, make that case. I sort of doubt that's going to happen. But it might.

In the meantime, make your best case, but realize that I'm going to act as a spokesman for all the agency. Our scientists have internally gone over this process, and they're continuing to do so. CBER has been very clear about the needs that they have. I find these legitimate needs, defensible needs, supportable needs.

So I'm not sure that we're saying different things, except that you've looked at the first center, you see this, you want to make sure that we recognize this. I may be putting words in your mouth and I don't mean to.

DR. BENET: Mike, you would never put words in my mouth.

But let me say, that the report -- I

don't disagree with what your scientist said and what your committee viewed. We all in this committee here, the Science Board, very strongly believes in the importance of science within the agency. But our report will differentiate the importance of laboratory science within the agency, and we do believe there are differences of centers in that aspect.

No one believes that there are differences in the need for science within the agency as a whole. But I do believe, and this committee will make strong recommendations relative to laboratory science.

DR. FRIEDMAN: Didn't you also review some of the clinical sciences? I thought you also reviewed the statistical and epidemiology component; I think he did.

DR. BENET: Yes.

DR. FRIEDMAN: And that's very valuable. I don't want to preempt your report, but my guess is you're going to say that there is some excellence there and the resources that

are needed there as well.

So with all due respect, it's not just the wet laboratory scientist. As good and important as that is, and don't let my remarks be misunderstood -- 1 think those are terribly important, but my guess is that what you're going to say is that wherever there is essential quality programs, that those deserve proper support. And I'm going to agree with you if that's what you say.

DR. BENET: Okay.

DR. KIPNIS: Thank you. We'll go on.

Subcommittee for CBER Review

DR. BENET: Thank you, David.

[Overhead]

I had the pleasure, over the past five months, of chairing a very prestigious group of 25 scientists and myself, who carried out a very vigorous review of the Center for Biologics; and the report is available to the Science Board, and I will review the major issues in the report for the committee at this time.

[Overhead]

1 thought it would be worthwhile reviewing the process. CBER proposed the appointment of an external peer review committee to the Science Board as a subcommittee on September 15, 1997; and in its September 30 meeting, the Science Board concurred. This committee was appointed in December of 1997. In January of 1998 all committee members received six huge notebooks of documentation to review prior to a four day site visit of CBER on the NIH campus, which was held February 3-6, of 1998.

The committee reviewed one partial and two complete drafts of the report, and has unanimously reached consensus on this report which we are presenting today to the Science Board as indicated here.

[Overhead]

My slides are being shown by Dr. William Fries, the acting Chief of Scientific Advisers and Consultants at CBER. Bill served as the staff for the committee, and I greatly

appreciate all of the hard work that he and all the members of his group in facilitating our ability to put that report together.

The report consists of 12 pages of public recommendations; a two-page introduction, a one-page preamble, three-page background and justification, three pages of crosscutting issues and three pages of summary assessments of the individual divisions within CBER which we reviewed.

There are three appendices, a committee roster, the letter of appointment, and the full schedule of the site visit report that are also included as Appendices A-C; and there's an Appendix D of nine pages which includes written comments of review committee members that were not included as text within the report itself; and we'll see as we go through that these are related to some particular overall issues, and give you an understanding of different viewpoints on the committee, but the strong sense of the committee members in this consensus

recommendation .

[Overhead]

There are also appendices E through N, consisting of 41 pages which provide detailed evaluations of each of the divisions. The summary of the divisions indicator on pages lo-12, the summary assessment.

We anticipate that the publicly-distributed document will be these first 37 pages, and the 41 pages of the detailed evaluations will not be publicly distributed, since the report contained evaluations of individuals; it's just as if a site visit was carried out and each individual scientist in many cases, are reviewed.

I assume, though I don't know it will work, but I assume that this can be obtained through Freedom of Information, but then there will be deletion of individual names that will be available. But the public document, Susan, will be available at the conclusion of my report to people in the room.

DR. KIPNIS: Outside the meeting room.

DR. BENET: Outside the room. It is already available.

[Overhead]

Let me go to the next slide which is from the introduction, paragraph 2, line 4, and it is important because it reflects what I just said to Dr. Friedman.

It also became apparent to the committee, which, including outstanding scientists from academia, major pharmaceutical companies, the biotechnology industry, national health institutes; both representatives from the U.S. and U.K., and research foundations. It was necessary for the committee to go beyond its specific charge and address the committee's unanimous concern that inadequate funding for CBER, particularly the inadequate funding for laboratory research within CBER, would risk potential damage, not only to the health of the population of the United States, but also the health of our economy by affecting an industry that will rapidly expand in the 21st Century.

Thus in structuring its report, the

committee details within a preamble our great concerns related to inadequate funding of CBER, and recommendations attention to this issue not only by CBER and FDA leadership; but also by Congress, the administration, the Department of Health and Human Services as well as the pharmaceutical and biotechnology industries and the public, whose health will be at risk.

[Overhead]

On the next slide I give you an overall summary of the membership of the 26 members, and their listing is in Appendix A of the report. The committee was composed of 16 academics, 3 representatives of what we would call the major pharmaceutical industry, three representatives of the biotech industry, 3 individuals from the national health institutes, and 1 from a foundation. Of the 26 committee members, six of them were member of the Institute of Medicine of the National Academy of Sciences.

[Overhead]

When you look at the individual

division reports, you will see that this is not a committee that uniformly liked what it saw at CBER. There are very hard-hitting comments, both in the summaries and in the individual reports about negative aspects of what we viewed within CBER and recommendations of things that need to be changed.

I make that point because the unanimous recommendations that we made reflect individuals who have very strong opinions in terms of the science itself but are unanimous in their view of what's important in terms of funding laboratory research within this agency.

Within the introduction also, just in a summary that appears on page 2 of the introduction. Just finally, a brief assessment of each of the individual divisions is presented in pages 10-12. More detailed evaluations of each division are presented in the appendices. These contain internal program reviews, and in many cases contain evaluation of individual research scientists; therefore they will not be distributed outside the FDA as

part of the committee's report.

These appendices were prepared for FDA CBER senior staff, and therefore as much detailed information as the reviewers wished to provide has been retained in the appendices with only minimal editing. These appendices do not follow a preset format, and reflect the evaluation concerns of the individual committee members; and these appendices are available to members of the Science Board.

[Overhead]

The first paragraph of the preamble indicates: It is the general consensus of the review committee that the issues we are evaluating here have major health implications for the United States. Inadequate funding of CBER can be predicted to lead to a crisis in terms of health outcomes as well as a crisis of confidence in the ability of our national regulatory authorities to maintain health, since the therapeutic, prophylactic and diagnostic agents, about which CBER advises and regulates affect all aspects of the well-being

of our population.

These areas of CBER concern include vaccine in all age groups with particular concern for children and the elderly. The biologic diseases that are of great importance to us as a population such as AIDS. The safety of the blood supply in this country, and the identification of infectious agents that could contaminate various products that are distributed to large portions of our population.

We go on in the second half of this first paragraph: In addition, the Center for Biologics, Evaluation and Research at present regulates the most rapidly expanding sector of our drug industry; facilitating the United States to be the leader in the development of new technology and new products that relate to biologics. This industry is an important financial component of our economy. It is the consensus of the review committee that for our industry to receive prompt and appropriate regulatory reviews, as well as for the ability

of our regulatory agency to respond to urgent needs, it is of utmost importance that the scientists in CBER have research capabilities at the cutting edge that allows them not only to understand rapidly expanding methodologies to evaluate vaccines and biologics, but also so that CBER's scientist-reviewers can interact with their colleagues in industry on a knowledgeable, scientific and technicalogic basis so that the appropriate recommendations can be made.

It is the consensus of the committee that CBER requires a strong laboratory research focus and not a virtual science review process. Otherwise, we risk the potential to damage not only the health of the population of the United States, but also the health of our economy in terms of an industry that in the 21st Century will expand by leaps and bounds.

Further on in the preamble, the committee recommends to the Congress, to the administration, to the HHS and to the Food and Drug Administration that it is greatest

importance to provide the appropriate support in expanding funding to CBER so that cutting-edge research and cutting edge scientists continue to be attracted to work in an agency that is so central to both the health and welfare of our economy.

We urge those reading this report to recognize that the cost-effectiveness of the products and functions regulated by CBER is enormous . There is no doubt that the major financial savings which we will make in health economy are in the area of prevention. It is CBER within the Food and Drug Administration that regulates and approves vaccines which the committee recognizes as the leading contributor to preventive medicine.

[Overhead]

Continuing on in the preamble: The review committee, in expressing its strong support of the need for laboratory research in CBER recognizes that this position is contrary to the experience of the agency and the industry and the review and approval of drugs

by CDER, the Center for Drug Evaluation and Research.

This position also differs from the perception of Pharma, in the recent renegotiation of PDUFA, the Prescription Drug User Fee Act authorization, who felt that the regulated industry should not pay for CBER research. However, it is important to recognize that biological are different from drugs . Drugs tend to be low molecular weight substances, capable of complete physical-chemical characterization which defines product quality and which provides a basis for production of consistent, safe and effective product.

In contrast, biological tend to be high molecular weight substances which are less capable of complete physical-chemical characterization ; therefore, product quality depends on in-process control and process validation to a greater extend than for chemical drugs.

Continuing on in this comparison

between drugs and biologics within the preamble: Manufacturing methods for drugs can generally employ non-physiological processing conditions which provide an effective barrier to product contamination by adventitious contaminants.

For biologicals, the dependence of biological function on delicate physical structures usually prevents the use of harsh processing conditions which are typically employed with chemical drugs. Thus, some biologicals have historically been associated with adverse reactions and death related to adventitious contaminants, particularly for those products with little opportunity for removal or inactivation of adventitious agents.

Again continuing in the preamble: The committee believes that a credible emergency response by CBER to adventitious agent problems associated with marketed biological products, including blood and blood products required immediate availability of a laboratory-based team of experts who understand both the

potential adventitious agents involved in the scientific manufacturing control and clinical aspects of the product.

I'm sorry; the last three came from the background section which justifies -- that comes from the background and justification for the preamble. So these were why we made these recommendations .

[Overhead]

We conclude this justification: In summary, this review committee echoes the views of our predecessor FDA Science Board Subcommittee on FDA Research, that was convened and chaired by Dr. David Kern, by affirming that the FDA, through a vigorous, high-quality intramural program of scientific research provides the essential foundation of sound regulatory policy and performance, and ensures that the FDA is and will continue to be in the best position to carry out its statutory responsibilities to protect, promote, enhance and affirm the health of the American people.

In light of the need for a vigorous

cutting-edge modern research program, the decrease in the agencies "and particular CBER'S budget in both dollars and full time equivalent staff is a major concern. The review committee believes strongly that depleting the agency's base of intramural scientific expertise must inevitably compromise the quality of review and regulatory activities as well as potentially adversely affect the health of our population and our economy.

Basically, the preamble and the background justification are for this overall view of funding of science within the agency and our strong belief that the science, laboratory science in CBER is different than in many other areas and cannot be carried out effectively with a virtual science program.

We then went on, in a series of crosscutting issues, that the laboratory science in CBER is different than in many other areas, and cannot be carried out effectively with a virtual science program.

We then went on, in a series of

crosscutting issues -- and I am not giving you the entire report, I'm just giving you some highlights from it -- in the crosscutting issues, in recommending support for a strong laboratory research focus in CBER, the committee recognizes this research must be mission-oriented and complementary to the laboratory research programs of the regulated industry, rather than duplicative of the research ongoing within the industry.

Particularly, we indicated that there was one area where we felt it was extremely important for laboratory research to be within CBER; that is in fact why you need this research in CBER and it is not at all duplicative of the industry, and that is in this paragraph.

It was recognized by the committee that a laboratory research function of CBER, which is critical to the maintenance of competence of agency scientists relates to analysis. Through the agents that CBER regulates and discovers in its own laboratory,

this agency has available a critical set of macromolecules for analysis and characterization .

Both the world and the agency are in serious needs of methods for characterizing, measuring and monitoring these agents. Efforts to develop these methods are not what they should be at CBER, probably for budgetary reasons.

We believe that CBER needs to be among the best regulatory agencies in the world, and proactive in responding to the needs of society and of manufacturers. The committee recommends that CBER create a new measurement science unit. That goes on in much greater detail within the report.

[Overhead]

These are other areas, crosscutting issues: The committee strongly recommends that CBER institute an approach to quality assurance of controlled testing, and that CBER create and evaluate standards for measurements carried out within CBER research that are commensurate with

what CBER expects to see for data that are submitted to the agency by the regulated industry.

The committee also noted that the statistical criteria which CBER scientists set for themselves are far below the standards that the agency requires for the regulated industry. The committee believes it is important that CBER use appropriate statistical criteria in evaluation of their own research data, and note a general lack of interaction of CBER laboratory scientists with their statistician colleagues.

In the design of studies to validate assays and to analyze the results of the animal model work, CBER scientists should have statistical input prior to carrying out the studies. The committee believes that a small group of two or three statisticians should be dedicated to supporting laboratory science presently ongoing within CBER.

Further on in the crosscutting issues: The committee recognized that there are

greater communication problems within CBER than have been recognized by the senior administration . One aspect of this communication problem is the lack of recognition of duplication of research in different areas, or at least recognition that different scientists, working on the same project, are often not communicating. The committee is also concerned about the esprit de corps of the group itself, although the committee recognized that some of this dispiriting attitude relates to financial cutbacks leading to FDA downsizing of science at a time when the climate for strong support of science at NIH is markedly improving.

Within the crosscutting issues, we actually spoke directly toward the budget to give you some awareness of what has happened in the budget. The committee recommends that the research budget be restored to at least 1994 levels. In that year the CBER research budget was $18.4 million of a total CBER operating budget of $44.5 million. This excludes

salaries for full time equivalent scientists.

The corresponding figures for fiscal year 1998 are $6.9 million for research budget, and $25.4 million of the total operating budget . In addition, new money will be needed for new initiatives such as the measurement science unit recommended here and new strategies that can enhance the program as well as providing funds for special purposes.

Then at this time within the report I've basically given you some of the text from the introduction, the preamble, the background and justification and crosscutting issues; I will not give any of the details of the individual division reports, but there are now three pages summarizing each of the divisions and our recommendation for those divisions.

[Overhead]

Following that is appendix D, which is the last slide. In preparing the committee's report, a number of insightful comments provided by committee members were not utilized directly. Since these comments provide further

understanding of the committee's views and rationale for the committee's recommendation concerning the need for funding of laboratory research at CBER, 16 of those comments are appended here under three topics.

The first, research is a central part of CBER's regulatory role; two, the mission relevance of research at CBER; and three, research efforts at CBER and federal funding of science.

So Mr. Chairman, I provide the entire report to the Science Board. We enjoyed our opportunity to review CBER. I think we have made some tough recommendations , but I think our report is in agreement with our previous position of Dr. Kern's committee in terms of the need for vigorous science, and particularly within CBER of laboratory science within the FDA. Thank you.

DR. KIPNIS: There are two other members of CBER here, Dr. Kathryn Zoon is Director, and Dr. Neil Goldman, Associate Director for CBER, who might wish to also make

some comments .

DR . ZOON : Thank you. One, I would personally like to say thank you to this committee and especially to Dr. Les Benet for the tremendous effort that was involved in this review. I'd also like to thank all the committee members; in particular Dr. Tom Waldman who cochaired with Les during the site visit.

This is a very, very important review for our Center. It has been enormously important, not only for us in terms of helping us to focus priorities at CBER at a time when resources are becoming very limited, but it also is very important because as this report suggests, the importance of the work at the Center for Biologics is incredibly important in the public health realm.

This committee spent four what I consider grueling days hearing many, many presentations by a large number of our investigators across all programs of the Center; and they included our laboratory-based

programs and as Dr. Friedman alluded to, a number of our non-laboratory research programs.

The comments that we received during the course of those discussions were on target, very thoughtful and insightful. We got a lot of good feedback during the course of those discussions that I think have been helpful already.

I'd like to say that I'm not going to respond to the report now because I think such a report needs to have a very thoughtful and appropriate response. We will do that at the Center; senior management will take this, look at each of the issues, prepare an action plan and a report which we will provide back to this committee and present to this committee at the time you believe is appropriate.

I just want to say that from the Center for Biologics, we believe that this will help guide us in our resource planning; and two, we believe it's very much on target with our strategic plan. And we are very grateful to all of you for this opportunity. Thank you.

Neil?

DR. GOLDMAN: Yes, I'd also like to echo Dr. Zoon. I could not thank the committee enough. This was a grueling experience, if only at the beginning when we sent you those six huge books of information to read; and then to go on to those four complete days.

I think I'd like to add to what Dr. Zoon said that this in fact has been enormously valuable process, review process for us. We are having to look in a very demanding way at how we use our current resources, and your advice is going to be critical to that use.

That in fact was part of our strategic plan, to have a committee that actually overviewed, at an upper level, the actual research that went on. So the total research program. And then to utilize that for doing prioritization, this is very helpful to us.

I'd like to think that this process in fact should not end; that this is similar to a process that is actually ongoing at NIH where they are, they have their institutes reviewed

every ten years, in a similar manner at an upper level. I would hope that that's the case here , that we maintain this oversight.

It's critical to us, as Dr. Blout and others had mentioned, in terms of getting the message out that we do research in that it's important to the FDA; and that the FDA understands its importance. I think it is critical that we have an oversight committee that reaffirms this.

I'd also hope that part of that committee may go on to be a more maintenance-type committee that would provide counseling to the Center on a more frequent basis, maybe every six months or so. And I think Dr. Schwetz will be talking about that when he refers to peer review.

I guess ultimately I think that this was valuable to us, and I agree with Dr. Friedman that you didn't have an opportunity to see the others; and I would think that that's something of a challenge that he's made to this committee, and in fact you should be looking at

all the other centers in the same light, with the same amount of criticality.

So I hope that his concerns are taken seriously. So again, I would like to thank the committee for an outstanding job.

DR. KIPNIS: Thank you.

Dr. Blout, do you have any comments?

DR. BLOUT: Yes. I want to add my word of thanks. You did an outstanding job, and we're all grateful for it. But it's only the beginning. And after lunch we should at least think about where we go from here.

I don't want to see this report buried; and how do we get the word out in a way that's most useful to CBER and the agency?

DR. KIPNIS: I, too, I think I speak on behalf of all the board members, this is an extraordinary report and you and your colleagues I think are to be congratulated.

What impressed me as I read through the whole report, which is substantial, was the willingness to make very candid comments but not get lost in some of the details of

positivity and negativity in terms of the overall conceptualization of science and CBER and where it should be going and what resources are needed, what organizational recommendations should be given serious consideration. I thought it was really extraordinary.

Also, the next issue relates very well with what just has been done; namely, peer review in the system so it allows a certain continuation of the generalities of the report to be considered; and I think also a break would give other members an opportunity to formulate some concrete questions that can be raised before we bring recommendations to the Board for acceptance.

Dr. Cuatrecasas.

DR. CUATRECASAS: I'll make a few comments that will throw a little bit of cold water on some of the euphoria. The global issues that Dr. Friedman spoke about previously, and independently it really did disturb me because I think overall it's possible this report could be counterproductive

to the overall process of what we're trying to achieve.

The specific charges given to the committee are very clearly stated in Kathy's letter from December 22, and they don't have to do with justification or rationalization of the research, or how critical the research or the activities of the division are to public health, to international health, or all of the wonderful things we heard about.

They had to do with devaluation of the current research programs; and specifically, more specifically, they are all very clearly spelled out. But the evaluation of the research programs for their scientific quality, mission relevance, and scientific management and leadership. That's it in a nutshell.

Now, that was done, and I think that was done admirably well and is very valuable. Those parts of the report I found extremely useful and I would think that the agency would find very -- the center would find very useful.

The problem I have is that the major

thrust of the report is in the beginning, and the parts that are highly editorialized in a global sense; and I think these are in contrast or in contradiction to David Kern's committee, to their recommendations.

The committee struggled for a year, year and a half, with science at the FDA. Not CBER but laboratory science was debated and discussed. I was a member of that committee. We struggled and we came to the very strong conclusion that we had to strengthen the scientific base across the board; the technology, the science, and the laboratory across the board.

Now this report seems to me to try to distinguish CBER from the others. Certainly there are differences -- I will not debate that; there are differences. But in singling out those differences and seeing how unique they are, the implication is that the others are not so important. And there are some specific areas where there's almost an admission that the other centers do not need

laboratory science, and they don't need the same kind of scientific quality as CBER.

I think this has been based, not on an incorrect assessment of what CBER is doing, but in ignorance of what the other Centers are doing.

There are a series of justifications which I think are contrived. The notion that this is the major area of health prevention because of vaccines, that's okay if you're thinking 50 years ago. But now, can we say that the activities of CBER are more important in prevention than food and nutrition, than avoidance of carcinogens? Can we say it's more important than prevention of diabetes, early detection, or tied to diabetes or Alzheimer's disease, prevention of cardiovascular disease?

We're in an era where the tools that CBER is using and the tools of biology, the tools of genetics, are not being applied in a preventive measure, in a preventive way across the board. And also not only in human areas.

This is just one example; we can go

on . The other uniqueness that is claimed is a molecular one. Now, I can't accept that laboratory science should be greater than CBER simply because the molecules are big and the other ones are small. I mean, it has to be based on the biology, the medicine, and something more fundamental.

The big molecules, the polymers, the DNAs , the proteins, the -- within small molecules, there are very many -- there are molecules that may be genotoxic, molecules that are small, that have uniqueness just as much, because they can integrate into DNA or into genetic material. It may have long term consequences. Is that less important? Just small molecules are steroidal molecules; they're also equally difficult. They are molecules that are made by fermentation. They are small molecules, they're also very difficult to produce, if we talk about production.

Certainly you can't deny that there are unique aspects to producing and

characterizing proteins, but they're equally unique features about other kinds of molecules; so please let's not say that those things justify vis-a-vis other centers and other activities.

So I'm a little concerned that if we do this for all the other centers, we're going to come up with a bunch of reports, each one beating their drums, and we're not going to get anywhere .

I think as Michael said so eloquently, We have to address the fundamental issues of how do we elevate the quality of science for the FDA. David Kern's committee emphatically said that to do that, we need active scientists in the FDA, and we need them everywhere. Some places will be more than others, of course; and each center, each division, will have its own character, its own differences, and I think what we need to do is to respond to that.

But those are the aspects that concern me . I present them dramatically --

DR . KIPNIS: No, no, Dr. Cuatrecasas;

I think that the comments you made are very valid. It is the inevitable problem when you have one unit to review that the certain element of focus evolves on that element when other elements also have to be reviewed.

And I think what Dr. Blout has pointed out is the critical need for the chief scientist; because until you have an organizational structure where there is a chief scientist who then in essence, he or she, imposes a demand on every element in there to contribute as a part of the whole instead of conceiving themselves as the whole initially, I think that that's going to be a major role that that chief scientist has to play, as an advocate of the entire unit rather than advocacy on an individual base.

On the other hand, it's certainly natural to anticipate that every director of every Center is going to have a certain agenda to impose the needs of that Center. So I think that will be the evolution that would occur.

DR. CUATRECASAS: Absolutely.

DR. KIPNIS: But I do think that the issues do have generic qualities; and I think that it will be important for this committee to acknowledge that this is a focal report that raises the issues that have to be addressed on a much more broader base. But there are legitimate requirements for CBER itself that have to be addressed at the same time.

I think it best if we break so we all have time to think about some of the comments we make, because they do lead into the peer review process, which has to be total institution.

DR. BLOUT: What time do you want us back?

DR. KIPNIS: Due back here at 12:30. Try and make it even earlier if you can.

[Luncheon recess; 11:44 a.m.]

AFTERNOON SESSION

[12:45 p.m.]

DR. KIPNIS: I would like to call the afternoon session to order to order, for the Science Board. There were two things that the Chair neglected to do that has been brought to my attention.

One was to ask the committee whether they accept the Toxicology subcommittee report to proceed with the plan as presented.

Is there any discussion?

We need a motion.

[Motion.]

DR. KIPNIS: Is there a second?

[Second.]

DR. KIPNIS: All in favor?

[Voice vote.] [Passed.]

The next was, should the Science Committee accept the recommendations of the Biomaterials Forum not to proceed further because of the discussion that ensued, with the explanations being offered.

Is there such a motion?

[Moved and seconded.]

DR. KIPNIS: All in favor?

[Voice vote.] [Apparently unanimous.]

DR. KIPNIS: I would like to add one addendum, if it's agreeable; and that is that we ask the individuals involved, particularly at the FDA, to give us a follow-up sometime next year or the end of this year as to what is happening in this arena so we keep informed.

Then we will continue with the CBER review. Are any additional comments that the committee wishes to make vis-a-vis the CBER review?

DR. CUATRECASAS: I just want to perhaps clarify my comments, because it's possible again in the end that I was trying to be fairly emphatic. And I didn't want to project as totally negative.

It's a very valuable report, and I think a few minor editorial changes, a few minor editorial changes in the beginning, particularly those that would imply that there are other divisions, other centers of the FDA

that do not need perhaps similar kinds of things .

So the uniqueness within this is such that it needs research above any of the others, I think to remove that kind of information. Otherwise, I think the report is a model, and the substance of it could be used, I think as a model to show the integration of good science with good regulation.

DR . KIPNIS: That's the way I think many of us -- 1 took your comments in that context, that this is the format that can be used for a more systematic review, and that it could be very useful for the future chief scientist to have this kind of database available to whoever sits in that position to adjudicate the kinds of natural competition for resources that any institution would have.

I would like to make the suggestion that now that the final report has been given to us today -- by the way, your old reports, if you brought them with you, can be left behind in the box which will be shredded; but take the

reports with you. And I would like to have each of the members of the committee then submit to either Dr. Blout or myself whatever additional editorial comments or modifications you felt appropriate that we could then incorporate and then check with all of you to see if that's acceptable before final action is taken on the report.

DR. BLOUT: I wouldn't think we'd have to send you the whole report; we'd just send you any modified pages, if that's satisfactory. And as I've said to Les, I'd like to see a little more emphasis on what CBER has done right out front so that we can use this in a way that's appropriate for the agency to use it.

And I'm counting on Dr. Zoon and Dr. Neil Goldman to give us that kind of material.

DR. KIPNIS: Is that agreeable with the Science Board?

DR. BLOUT: It's up to the Chairman.

Les, is that okay with you?

DR. BENET: Yes, that's fine.

DR. KIPNIS: Then we'll go ahead with the program; Dr. Bern Schwetz is going to present --

DR. BENET: I'm sorry; I would like to make some comments in response to Pedro's comments --

DR. KIPNIS: Of course.

DR. BENET: -- and to everyone else, and justify why certain things are in the report and what's the feeling, concerns of the committee.

I think most of you are aware that I'm not an expert in CBER. There were 25 experts in CBER on this committee, and the report reflects the strong feeling of the individuals in the areas of biologics.

The report includes the wording that includes, because this is the wording that the committee wanted to have there. But I think it is important to respond to Dr. Cuatrecasas' comments and to at least give you the reasons why some of these points were there that you find objectionable at the present time, or of

concern at the present time.

There was a recognition within the committee, and certainly from the industry members on the committee, that maybe the biologics community had not paid close enough attention to what was happening in the PDUFA reauthorization . Because one of the real impetuses for Dr. Zoon asking for this report is the necessity for cutting in essence her science budget in half and her scientists within CBER in half as a reflection of the PDUFA reauthorization.

Committee members strongly felt that there was a difference between biologics and other issues that come before regulatory agencies. And they wanted that information in there. So they felt it was most appropriate and necessary to contrast biologics with drugs, for a very important reason; and that's why that information is there.

The PDUFA original five years and the reauthorization recognizes the accomplishments of the agency, particularly the Center for

Drugs, in rapidly approving and lowering the waiting time and meeting the guidelines and goals that were set for the agency in terms of their review process with the idea that this money would be utilized to increase the number of reviewers within the agency and not be used for other purposes.

So there is a record of great accomplishment; and in my mind, that accomplishment is primarily in the area of drugs .

When the Science Board heard the recommendation from the subcommittee that Dr. Cuatrecasas was a member of, in terms of the importance of science within the agency; everyone believes that and thinks it is correct, but there was basically no justification in that report for why we needed science in the agency.

And the members of this committee felt strongly that they needed to say why we needed science in CBER and laboratory science. Because it was apparent that drugs succeeded

through the PDUFA in essence in a virtual science environment . There is not large amounts of funding for laboratory research, and a virtual science environment concentrating on biostatistics, on epidemiology, on clinical aspects, seemed to have done very well.

Their concern is that a virtual science environment in biologics will not work, and that is why this report was written in this way; and perhaps I did not do a good enough job in pointing that out. They feel that the science in biologics is moving so rapidly and that the technology that is changing in terms of the information that scientists within CBER must have to do a good review is that if you are not doing this science, virtual science will not suffice.

And that is their position. They pointed out that since virtual science has succeeded in drugs, that although I can understand the concerns of this Board, and this Board is going to make its own recommendation , the members of the committee felt strongly that

they needed to differentiate what was the issues in biologics versus the issues in drugs; and that's why that information is so hard-hittingly put within the report.

So it is the committee's belief that this is something that has the potential to be a crisis. And they do not want to have to face reviewers within CBER who are not at the cutting edge of the science. And their strong feeling, not necessarily doing the same science, but doing laboratory based science that is concentrated on the measurement aspects of what is being evaluated here is where the emphasis was in this report.

So I can understand Dr. Cuatrecasas' concern; I can understand the concerns of the Science Board, but I wanted to reflect to you that these were not issues that were not considered. And it was strongly felt by this committee that it necessitated a differentiation between the types of science that is done at least in drugs and in biologics and by expansion from that, probably in other

agencies, also.

I personally do not feel, my own personal comment, that it's going to be possible for us to have an effective recommendation if we suggest that science is the same everyplace throughout the agency; I do not believe that. And the group of people that Dr. Friedman talked about in terms of making these recommendations , that everybody needs laboratory science; I agree everybody needs laboratory science. But I think that there are big differences in the kinds of science that you need and the expertise you need in the different divisions, and that's reflected in this report.

DR. KIPNIS: Any comments, Pedro?

DR. CUATRECASAS : Well, my view is that the activities and the value of CBER stand on its own merits. Independent of what was happening everywhere else within the agency. Within CBER there are differences among the divisions, and they do not all require the same kinds of laboratory expertise that you're

describing.

The kind of assessment and scrutiny which has just occurred for CBER has not been done with the other centers. So how can we judge? We touched other areas which have equally rapidly moving scientific breakthroughs . A large number of the things that are happening at CBER are going to quickly be applicable to neuroscience, they're going to be applicable to bacterial diseases, they're going to be applicable to all kinds of things, and your divisions are going to be blurred.

so there's no need, I think, to exalt the scientific need of CBER as something unique insofar as it reflects on other centers of the FDA. So that would be my only point, is that the uniqueness that you describe, yes; but every other center is also unique.

DR. KIPNIS: I'll just make one last comment , if I may, and that is that the organization of the FDA into centers implies heterogeneity of needs. Otherwise, why have different centers?

I was discussing with Dr. Blout, what happens when potatoes are used as a source of vaccines? It's going to be the Department of Agriculture and the FDA are going to be involved in that. What happens when proteins are isolated from tobacco leaves that are going to be routinely used as drugs? Is that going to be Agriculture or is that going to be the FDA, and who in the FDA?

So that the issue of science per se is critically important, and we all recognize that science is not homogeneous and that -- well, it is in a generic sense, but what does it mean to you , scientific method? But the details of science will reflect what is for that time the major domain of one of the activities within. But we also recognize, even in the report that I think was well written by Dr. Benet, even there the capacity of one division to talk to another division and interact is critically important because they're sometimes replications, some of which are good and others of which would be less good than could be

existing elsewhere.

So I would think that the comments made on the report will be more in the -- not in the substance, but in the effort to get across that here is something that should be employed throughout the system in terms of peer review, so that eventually a coalesced presentation for the needs of science can be made to the agencies that we're going to be dependent upon to support this, which is primarily, it seems to me, Congress . But Congress' receptivity will certainly be exacerbated and sensitized if the public also accepts this, as does industry.

So I would think that the editorial modifications would be more focused on -- this is used as an example of what can be done rather than as an endpoint in itself.

Does that reflect -- that's I think a critical point that should be made. If that's agreeable, we will now go on to the next session in which Dr. Schwetz will present Science at the FDA. Unfortunately I will be

leaving in about 25 minutes, and Dr. Elkan Blout has with graciousness accepted the responsibility of carrying on in my absence.

Peer Review Process

DR. SCHWETZ: Thank you, Dr. Kipnis. Before I proceed on to the discussion of science at the FDA, may I come back to one other point of the peer review process, and ask for some additional input?

The assumption is that we are going to proceed through other centers with the peer review process similar to what has been done within CBER. But what I would ask of you is whether or not you could provide us either from within the committee itself or from the Center or from the other Science Board members for any additional input in how it should be done differently in the other centers in the future.

There are a lot of dimensions of this that we ought to examine one by one; the amount of information you received, the number of days it took, the level of detail into which the reviewers went to get this picture of the

Center. How could we get a broader comparative view of what's going on within multiple divisions within a Center as opposed to a glimpse of 12 divisions fairly independent of each other.

There are a number of things that I think we need to consider as we design the review process for the next one.

DR. KIPNIS: Bern, I would also make the comment that I think the committee will have the chance to review the issue of peer. But I notice in the proposed peer review FDA structure, several of us don't believe that the position of the chief scientist is appropriately recorded in the hierarchical structure of what has been designed here.

Many of us thought that the chief scientist should have direct access to the FDA commissioner, and that the Deputy Commissioner for Operations implements what the FDA commissioner and chief scientist, and whatever executive group that is decides should be implemented; but not that the chief scientist

is sort of a homunculus to decide between the deputy commissioner.

I rely on others in this group to also make their comments; and you can put them into writing if you like, using capital letters.

DR. SCHWETZ: The chart that Dr. Kipnis is referring to is one that's in your tab -- under the heading of Peer Review Process. It's the chart that looks like this.

DR. CUATRECASAS: It's also, the description of chief scientist, the announcement of this. And David, this also strikes me, I don't believe it was the recommendation of the Kern committee; I think the recommendation was --

DR. BLOUT: He would sit beside.

DR. CUATRECASAS: -- very strong that the chief scientist should report directly to the commissioner.

DR. KIPNIS: Thank you for pointing that out. I agree with you wholeheartedly. So we can voice our opinions to whatever is ultimately decided.

But I agree; I think that as presently constituted, that's not what the Science Committee had for the position of the chief scientist.

DR. BLOUT: And that change could only make the position more attractive.

DR. SCHWETZ: As we discussed this internally, there are two things that I think need to be accomplished, if you stand aside from the question, for the minute of where that line is.

First of all, the chief scientist must sit with the deputy commissioners and the commissioner in deciding the overall policies within the agency. But the other part that has to work is that the chief scientist also sits with the center directors. Otherwise, the operating space between the chief scientist and the center directors will be such that there won't be any bridging.

so this was put together as a hybrid to permit the chief scientist to work directly with the commissioner on the FDA executive

committee, but to be sure that the chief scientist met with the center directors on a weekly basis on the business of the agency and operations.

So your additional input would be very welcome on this, but those are the two things that we were trying to accomplish.

DR. LANGER: I guess the question is, who does the chief scientist report to?

DR. SCHWETZ: For this chart, it's a direct line report to the deputy commissioner for operations. And that's what your question is.

DR. LANGER: Yes. Because I don't think anybody would question the other issues that you just raised. I think the question is, what I just asked.

DR. SCHWETZ: Yes. We'd welcome your further input.

DR. BLOUT: Who do the center directors report to? Do they report to the

to permit the chief scientist to work directly

with the commissioner on the FDA executive

DR. SCHWETZ: No. The center directors and the director of the Office of Regulatory Affairs report directly to the deputy commissioner for operations.

DR. LANGER: Right. My question was, who does the chief scientist report to?

DR. SCHWETZ: In this chart?

DR. LANGER: Right.

DR. SCHWETZ: And in the advertisement, to the deputy commissioner for operations.

DR. BENET: If I could just -- not on this issue, but to come back to some of the questions that Bern raised.

One of the real advantages of the committee that I had was the dedication of these outstanding scientists. And about 40 percent and maybe more -- Dr. Goldman and Dr. Zoon can correct me -- were individual scientists who had already participated in peer review process at CBER.

so we were not a group of people that were looking at science for the first time. We

had people with great experience who had come two or three times. I think that is an important part of this peer review process that a good fraction of the committee be very familiar with the science and be people who are regular reviewers.

Dr. Zoon or Dr. Goldman, am I correct on my percentages about that stuff?

DR. ZOON: That's right.

DR. BENET: So I think that's something that needs to be built into it, and that is why in four days, which was a huge task, but we were not operating with no background about the scientists and about the individual scientists.

In addition, one of the six volumes that we received had all of those peer review reports in it from the previous reviews of each of the divisions. So we had the opportunity to see previously what had been recommended within the divisions.

So Dr. Schwetz, I think that's a real important component of how you do this; not

only expertise within the group but expertise, continuing expertise to make such a report possible.

DR. KIPNIS: I think those are very good points you make.

Any other comments?

DR. CUATRECASAS: David, I think the only -- again, when I think about the role of the chief scientist and some of the things that that person would do, what comes to mind is the report we heard, the CBER report, was critical. And I think you said earlier, before we broke for lunch, what's going to happen to this; we don't want this to sit on the shelf, we don't want to keep this __ missing forever. You know, what would happen to it?

It could be used very effectively by a person very high within the FDA; ideally, the commissioner. Or possibly the chief scientific officer could do that as well. But if the chief scientific officer is working with the commissioner hand-in-hand, then I think the commissioner might be more effective, say if he

were to place this before a congressional subcommittee .

This is, also beginning to think about how do you carry this report forward and try to generalize it and try to catalyze more interest in a broader sense. One wonders whether -- taking this a step further, even whether a new commissioner should be exposed to this beforehand, one at a time, and seek his or her views on this report so that the concepts at least are from the beginning understood and also felt to be important in projecting them in original hearings, and back in the beginning so it doesn't just take the secondary, tertiary role.

DR. BLOUT: There's one other issue that hasn't been verbalized today, but is on the minds of some people. What is the relationship of the agency to the department? And to HHS and to the Department of Agriculture? And are they consonant with the view of the future of FDA?

DR. KIPNIS: I don't know, Dr. Blout,

if those discussions have gone on.

DR. BLOUT: Well, they're below the surface most of the time, but they're there.

DR. SCHWETZ: Elkan, all I would add is that I think this series of reports, this one and the ones that will follow, will provide extremely important leverage for the commissioner representing the FDA within the discussions at the DHHS level to try to get additional support through the Department level for the FDA.

This is leverage that has to be developed and used.

DR. KIPNIS: Okay.

Science at the FDA

DR. SCHWETZ: Under the heading of the science at the FDA, there are several comments that I would like to make specifically to the issues that are laid out here; and then I've got one transparency that I would work from that relates to something that you have within your packets.

The comments that were made in the

review of CBER are interesting in the context of the earlier discussions we've had about developing virtual science capabilities within the agency, because the sense up to this time was that in order to change one of the dimensions of the culture of science within the FDA is that we have to reduce the barrier between centers and have FDA scientists working more closely together in the virtual sense; that the scientists of the agency represent capabilities of the agency to address scientific questions.

And it's interesting, Les, to hear the strength with which your group reported that the that may not be, if I understand correctly, the way they would recommend that the science of CBER be handled.

So I think we need to think further what a virtual science center within the FDA means. One of the things that I've been doing in the past year is meeting with what I've referred to as discipline groups; but they're groups of experts within a specific field.

The statisticians, the people who are working in immunology, the people who are the neuroscience individuals and so on, through the chemists, the mass spectrometrists. Groups of this kind who represent areas of expertise that go across the whole agency; one by one I'm meeting with them to have them think as a team independent of center barriers, center lines, and to begin to think of themselves as an FDA resource; so that at times when we need help across center lines, we have people who are familiar with each other and know what the capabilities are elsewhere throughout the agency.

So to the extent that that gives us more of a virtual capability to meet needs that go across the agency, we are working on that; and we need to think of that in the context of this CBER report.

One of the efforts to make people better known within the agency to each other was the development of this expertise database, which we've summarized for you in the past .

We're now someplace, something in the range of 25, 30 percent of the people whom we'd like to have in this database are already in there. That's low and it's not high enough to make this an effective tool, but we have some centers that are essentially 100 percent into the database and others who are just starting.

So I have no thought whatsoever that we're going to peak out at 30 or 40 percent. We have to get that up to 80 percent or more so that this becomes an effective tool. All the centers in ORA are committed to put their people in here, who need to be in the expertise database; so we're continuing to populate that, and I would hope that we would make considerable progress toward that 80 percent level by the end of the year.

In the area of research tracking, we have now within the Office of Science collected the definitions of all of the research projects that are ongoing throughout the agency, and that's something between 700 and 800 individual research projects for which there is a protocol

and a PI and a title of a study and so on.

This for the first time has permitted us to analyze this database of some 700-plus projects to identify what kinds of research the agency is doing when you put all of the projects from across the whole agency together in one database and find out what percent of this has to do with methods development, what percent of it has to do with agent-driven research, what has to do with clinical studies versus nonclinical.

So we're finally at a stage where by default we can define what the FDA research agenda must have been, assuming that that relates to what we're doing. Now with this database in mind, I am scheduled in the near future to bring an evaluation of this collection of projects back to the center directors and the deputy commissioners to define for them what our research program looks like and to be a little more proactive in deciding that I would not have expected that 50 percent of our research projects have to do

with methods development.

Do we want it to be 50 percent or should it be more or less than that? So I see it as an important step toward moving us forward in developing an FDA research plan instead of a collection of center research plans that don't reflect a lot of integration with each other or a lot of conversation; not as much as we need.

So I think we're making progress on this. All of the new projects that are submitted for the next fiscal year, and that will be developed over the summer, all of those will be submitted in a format that we can build a database that's searchable and we can very accurately describe what the research program for the agency will be in 1999 based on these submissions that come in at the end of this year that represent next year's research.

We'd be happy to share that kind of analysis and information with the Science Board at any time you would like it, either for information or for discussion.

DR. BLOUT: I think it would be valuable, Bern, to share that because the magnitude and the types of projects are not known to the Science Board.

DR. SCHWETZ: Well, I would submit they're not widely known within the FDA.

(Laughter)

DR. BLOUT: And I'd agree.

DR. SCHWETZ: For example, for the first time we will be able to see which individuals are proposing work on Cyclospora, and who are they and where are they coming from, what's the title, what's the level of commitment to this project? To this time, we couldn't have guaranteed that we knew which projects were out there. You knew some of them, but you didn't know for sure if there was an outlier someplace and somebody working on it, and he wasn't communicating with the rest of them, you wouldn't have known it. Well, now we will.

So we'd be happy to bring that, if that's desired by the Board.

The other piece that I wanted to bring forward is a proposal that has to do with meeting some of the objectives that you've been talking about here today. And one of those pieces is to bring public input into the evaluation and the review and the identification of FDA priorities. So bringing the public input into this priority setting process.

The second objective, to receive input more formally from a full range of FDA scientists; and that would include laboratory researchers, non-laboratory researchers and reviewers; and the priorities for the research and the scientific issue is related specifically to the review responsibilities of the agency. So a second one is input from FDA scientists.

A third expectation for this proposal had to do with leveraging. At a time when we can't deal with all of the issues that surround the needs of the review process of the agency, how can we leverage information, how can we

leverage resources to a better extent to reach out to non-FDA scientists and resources to help expand the size of our research program to a larger extent.

A fourth objective of this proposal is, how do we identify FDA research and science priorities going beyond the individual center priorities. How do we collectively identify and define what the FDA research priorities are rather than in a prospective or retrospective manner as we've done it now?

Another objective then is, if we can identify what those FDA priorities are, then how can we reallocate resources to meet those FDA-wide needs, and then this proposal also shows you how the Office of Science fits in the middle of all these objectives to accomplish this. I'll work from a transparency.

[Overhead]

You have this table in your notebooks, and I think it's the last thing before -- .

If you can find this chart in your notebook so that you can follow along and write

down whatever questions you have on it.

This chart focuses on generating resources to be able to support the scientific program of the agency, and then how these funds might be used for support of this work. The other important piece of this is the identification of research and science priorities that take into account the public, the FDA scientists, research input from the rest of the components of the agency, to help develop that FDA research plan; and then the role of the Office of Science kind of in the middle of this, and then how this translates into support of individual research projects.

Let me start up here on the upper left talking about resource generators. This is one place where I think the agency should have more of an outreach program that formally brings in input from industry and from academic centers to review what there might be in terms of resources to get the work done that' the agency needs to have done to be able to anticipate the expertise needs that we'll have in the future

to deal with the pipeline of new products coming in in the future.

So when you talk to people on the outside, there are all kinds of foundations, there are research-supporting kinds of organizations; there are sources of money that the FDA has for a number of reasons not tapped into, some of which are questions of legality, of accepting money. But if we're going to reach out for opinions of what priorities are, and how it is to fund them, this would be one place where we could have some kind of a resource leveraging committee within the agency that would help bring to our attention what is known more broadly beyond the agency of how resources can be brought to bear to solve research needs.

One of the things that we have started in the last couple of years, more extensively than we've had in the past, is memoranda of understanding with other government agencies, including Institutes of NIH. Liz, did you mention the one that you have with the Dental

Institute earlier this morning? That's being increased widely, and we have a number of interactions with other government agencies where we agree to identify what the priorities are, and to the extent that that results in other means of support for FDA work, that's something that we need to recruit help from other government agencies to meet our needs and that's one way to do it.

One of the things that's been discussed several times within the agency that is being used with CDC and with NIH and with other health research organizations is the development of foundations, is what it's been referred to. Well, there's a lot of baggage that goes with foundations, and within the FDA there has been a reluctance to develop a foundation as a means of receiving resources from the public to be used for purposes within the agency.

so just to finesse the question of a foundation or not, I've simply put the word "alliance" that we would have some kind of a

mechanism whereby money could be received that could for example be used for training of FDA scientists regarding products of the future or whatever it might be.

This might not be used directly to support research, but it could be used for other functions within the agency that would permit our scientists to travel to the meetings that they need to to get the information or to afford other kinds of training; so this would be a mechanism where you'd have a body of directors for this alliance that would receive requests from the agency to support certain kinds of activities; and the decision would be made by them what things should be supported and what shouldn't.

DR. BLOUT: Bern, do you want comment as you go along on these?

DR. SCHWETZ: Yes.

DR. NESTLE: Alliance with whom?

DR. SCHWETZ: Sorry; I didn't hear your question.

DR. BLOUT: Alliance with whom.

DR. NESTLE: I'm asking who you had in mind as an alliance, and my question has to do with maintaining the integrity of the institution.

DR. SCHWETZ: The alliance itself would be a Board of Directors who would be responsible for this foundation or alliance, whatever you want to call it; and that would be the body that would officially receive resource allocation.

DR. NESTLE: My question had to do with, who are you expecting the resources to come from.

DR. SCHWETZ: They would come from philanthropic organizations, perhaps from industry, perhaps -- from individual people who wanted to supply money to some other research function. There's no limit there to where the money could be received from.

DR. NESTLE: I would be very concerned about the integrity of the agency in that situation. Why would anybody give money to an FDA alliance if they didn't want to influence

what FDA was doing in some way?

DR. SCHWETZ: Well, that's why it's an alliance and not money being given directly to the FDA.

DR. NESTLE: I'm not sure laundering solves the problem.

DR. SCHWETZ: That's the problem with foundations as they currently exist. And it's not clear that that laundering process is effective in making this an easy transition.

Dr. Zoon?

DR. ZOON: I think there's always a sensitivity to the issue of, are you getting something for something that perhaps might influence a particular action, whatever.

I think what Bern is looking at is a way to get resources that may have an opportunity to support broad programmatic areas; not an individual particular product. It may be a specific scientific issue that needs addressing that would cross-cut a variety of programs.

In terms of other -- and those

resources could come from industrial groups, they can come from private organizations, and in fact we often have people actually asking private individuals who've had some experience that they just want to donate money to further the action of the agency with no strings attached.

And I think the sensitivity to make sure that you protect from conflict of interest is very important; but I think in the climate of diminishing resources, we really need to think appropriately on leveraging resources and how to do that appropriately.

DR. SCHWETZ: There is another whole philosophy that says that we shouldn't go after these small amounts of money in a tin cup. We instead need to have appropriations to cover what the agency needs to do, and that appropriation needs to be large enough to permit us to do the work that the agency should be doing. As opposed to the signal that we're going to make up our budget deficit by virtue of tin-cupping. So there are two sides to

this.

DR. BLOUT: Dr. Sanders.

DR. SANDERS: But there are some things that you might like to do which, even if the government was of a mind to do so, they just don't have it in their brief to give you money for a particular resource.

The parallels with the NIH, which has created something called the National Foundation for Biomedical Research to receive funds in areas where the NIH funding itself cannot support particular programs, such as in the clinical scholars program; such as perhaps building a guest house for adults as they did for the children; things that would be specific to NIH programs but which the government won't pay for, Congress won't appropriate money for.

To the extent that this alliance fits into that particular model, I think it's appropriate; although I think Dr. Nestle's point is very important; that is, making sure that there is a clear Chinese wall, if you will, between the receipt of funds and the way

they're used.

DR. NESTLE: With all due respect, I would point out that this is a regulatory agency, which puts it in a particularly sensitive position. I don't think you can be too sensitive about this one.

DR. SCHWETZ: What you're bringing up is exactly the reason we don't have a foundation, up to this point. But what I'm trying to point out with this collection is that the agency has also not been very aggressive in exploring other opportunities.

So we've brought this up for discussion to be sure that there aren't some sources out there that would accomplish the objective of reaching out to constituencies who can help us not only identify good ideas of where we should be going, but sources of support as well.

And the support doesn't have to be just in money alone; it could be in information or it could be in other forms of resources.

Dr. Sanders?

DR. SANDERS: I think Dr. Nestle's point is very well taken; that is that this is a regulatory agency quite different from NIH as such.

One way of handling this rather than have FDA personnel man the alliance or whatever is to have a group of volunteers who are in the private sector handle it. So that they then could -- they could have a separate foundation outside of the internal workings of the FDA; that would allow some independence and maintain the security, if you will, of the FDA process and administration. But you've got to be very careful.

DR. SCHWETZ: Yes. To be sure, this would not be in the Office of Science, or would not be in one of the product centers. It would have to be distant; and even then the extent to which you could make it distant enough.

DR. SANDERS: But even the people who worked there, which shouldn't probably be paid by the FDA.

DR. SCHWETZ: I agree. That's for

sure.

DR. BLOUT: Bern, before we leave that whole box, tell us a little of who you'd see on the top line, the FDA resource leveraging committee. How do you conceive that?

DR. SCHWETZ: Well, it could be that this would be representatives from the major trade associations whose products collectively we regulate. So that would be one way to go, out to trade associations. Another one would be individual companies, if we chose to go that way, and universities.

So I've not sorted that out further, how we would reach out to the industry to be sure that all of industry who wanted to participate had an opportunity to do so; but still to get some who represented major portions of the industry. Some of you who know the industry better than at least I do today might well advise us on how we would reach out to industry in a way that would provide us with good input.

DR. SANDERS: If I could just speak to

that, I think that's even more delicate than the foundation.

DR. NESTLE: Thank you.

DR. SCHWETZ: I would just be very careful about that. I think that's a potential public relations nightmare. Maybe I state it too strongly, but it's just something that I think you have to be extremely careful about.

Even the user fee question; you know, we had to go through those. Since I've left the industry, I assume that those are working out reasonably well, but there were a lot of questions raised about that and making sure that the independence of the agency was being protected at the time. I assume that that has occurred.

But I think when you're looking at unencumbered funds that are being directly solicited from those that are regulated, it created some real problems for you.

DR. SCHWETZ: I would remind you again that this is specific generation of resources, not just money. And to the extent that this

would develop better collaborations with industry, to develop data jointly, and other mechanisms for developing information not just revenue to permit FDA scientists to cover the laboratory work.

More traditional sources of funds for the FDA to support this function are in the lower left, up here; and that would be the appropriations we get; interagency agreements, and we have a fairly large number of agreements with EPA and with institutes of NIH and with other government agencies to support work; cooperative research and development agreements that we have, providing support for specific research that's funded by portions of the industry, where it's approved within the agency that we can receive money for this particular research project from industry, to be sure that there's not a conflict of interest here, but within other product centers.

So we do have a fair number of these CRADAS that are in operation.

The receipt of grants is one that

we've talked about with the Science Board before, and I would remind you that within the FDA, FDA scientists can not be the primary investigator on a grant and receive money through NIH-types of funding, for grants, but we can be a coinvestigator and some other institution can receive the grant money, and we can work with that institution and receive support for example in their institution.

But at this point in time we cannot compete for grant money, but we can receive it with another investigator.

DR. BLOUT: And what are you arguing, that we should be able to receive grant money directly, or the scientists should be able to compete directly?

DR. SCHWETZ: The agreement that we're working under is an agreement within the Public Health Service. So there isn't a law someplace that says that we cannot compete for this grant money. This is an agreement within DHHS that people from within the FDA will not compete for this.

We've raised it for discussion in a large number of audiences, and while there is some agreement that FDA scientists for example should be able to compete for NIH grant money, it's really a mixed response. And there's everything from "we don't need more competition for grant money" to the fact that you don't have to write grants and you should use the appropriated money to support your research work" to other arguments, that the scientists within the agency feel that they can very effectively compete with others who are competing for grant money, and that they would be willing to compete for it, and would be a way of supplementing the resources, permit research to be done.

DR. BLOUT: I've certainly heard the argument that scientists within the agency can compete for grant money, but they feel hobbled by this Department rule.

Maybe somebody would like to speak to that. From the audience.

Dr. Zoon.

DR. ZOON: One of the areas that -- there's a balance of different proposals on the area of grants. And I think, I would say that scientists would welcome grants, or the opportunity at least to apply for grants.

The issue is, Bern, there are other agencies or other organizations that FDA can apply for for grants outside NIH and our scientists do do them and they have been successful.

There are some issues that I think are of concern to the National Institutes of Health with respect to giving grants within its own sister agency; and in fact I think they would prefer to work through the interagency agreement mechanisms as an alternative. I think the opportunities to look at this from a broader, maybe department level might be something they would want to reexamine.

DR. CUATRECASAS: Aren't there grants also from the IOM?

DR. BLOUT: Nothing significant.

DR. BENET: Bern, I can understand

what the concern is in NIH and HHS, because for example internal NIH laboratories cannot compete for the external money, so there's something in the budget that says "this is what we're going to do for science internal, this is what we're going to do for the RO1s, this is what we're going to do for every area. "

What my committee was concerned about is that there should be a line item for research within the FDA, and that this should be recognized as an important area, and that it's Congress that needs to recognize this; and that's what we pointed out.

It would be hard to imagine FDA competing for an NIH grant when NIH people can't compete for an NIH grant. So I don't see how that's going to work out unless it's done in some equitable manner throughout all of HHS.

DR. BLOUT: State your name and affiliation, please.

MR. EAGAN: Bill Eagan from the Center for Biologics. If I could just disagree with my center director for the moment.

As Dr. Benet has pointed out, research is intrinsic to the way we do business within Biologics. It's part and parcel of the process, and it really should be funded as such.

It should be funded as fully -- as, you need this many people, this is the salaries, this is what's needed for business, this is what ought to get funded.

I think many of these other mechanisms which we're exploring, we're exploring I think out of desperation, because the budget has been cut so much. And there are conflicts in all of these various mechanisms, including the CRADAS; they're not without their problems, either. That's just my own view on this.

The NIH has a somewhat different mission than we do; and unless we're going to refocus our mission to that of the NIH, there are problems with getting funding there as well. And I think you also have to wonder about or consider the, Congress has given so much money to this agency for its mission, so

much money to its agency for its mission, and then have some kind of internal equalization process, independent of what the Congress has allocated.

I think these are large problems in this area; and the simplest thing is to just have Congress fund what's necessary.

DR. BLOUT: Dr. Zoon again.

DR. ZOON: For the record, we don't disagree at all. My preference for any funding for the FDA would be appropriated dollars. I think we are in a time where we are trying to, because of the cutbacks in the support for research for FDA programs of trying to see how we can survive; and I think that in the context of this, we're looking at alternative ways to survive; and while these things are being ironed out and really a clear discussion of how this important work needs to be done can be accomplished.

DR. SCHWETZ: Thanks, Kathy.

With that, let me move on to other half of this, so that we have time to talk

about this as well.

A very important part of where we haven't been in the past is to have a broader input on identifying what the science research needs and priorities are for the agency. So this upper right-hand box is trying to pull together where we are on that particular item.

In addition to input from the commissioner and the Executive Committee of the FDA about what the priorities and future direction of the agency are, the input for developing the research agenda and the priorities should include the input from the chief scientist and the center directors and the associate commissioner for regulatory affairs; the field organization of the agency.

So there would be inputs sought from all of these, and there is now, but that could be more formal. The rest of this is something that is not quite as well developed. The possibility that we would form a research priorities committee, the Senior Science Council, is already in existence within the

agency, and it represents many of the people who were in the audience today that are the senior scientists from the laboratory and the review parts of the science of each one of the agencies, who sit together in this Senior Science Council on a monthly basis and discuss what's going on with the science and research of the agency.

Then to more effectively bring in the input from CAFDAS, the Committee for the Advancement of FDA Science, the junior scientists of the agency, and bring the input of the Senior Science Council and CAFDAS together, and include a more formal mechanism for bringing information in from the discipline groups that I mentioned earlier.

If we ask all of the microbiologists, what are the research priorities within the area of microbiology within the whole agency, and ask the statisticians and ask the immunologists and all of the people who represent cuts of a discipline of work throughout the agency, we would like to receive

input from these people who will see the research needs of the agency a little bit different than if you just asked them from within one organization, within one particular center.

To the extent that we would make that a bit more formal so that people feel they have input from throughout the agency into the priority setting of the whole agency, I think would be helpful.

To the extent that we had over here that we would look to industry for advice on how money and other resources could be pulled together to support research, you would also want to have some kind of a joint FDA-industry-academic group who would advise on the research priorities, independent of the funding process. That we have a more extensive outreach to get opinions from the groups whom we regulate and the groups with whom we interact on a research basis to get a more formal input into what the future of research and the science issue should be.

One of the things that has existed within the agency on a spotty basis; at least two centers have what they refer to as “science colleges” for training people. In particular, one of the things that we’ve been talking about is the development of an FDA science college that would be a voluntary organization of the scientists of the agency who want to band together to respond to FDA science issues. And collectively they might define the training mechanisms that could be used broadly throughout the agency.

CDRH and CDER have -- Drugs and the Center for Devices and Radiological Health have these now within their two centers; but this concept could be expanded so that there was a broader involvement in the training activities and a feeling of a broader availability of these training possibilities to any of the scientists within the agency, not just those two centers.

This would also be another mechanism where, from the Office of Science, we could

take questions to this science college and ask them to do homework for us to advise us on specific questions within the agency that relate to science and research.

Let me just talk a little bit about where the Office of Science fits into this. To the extent that we have memoranda or other mechanisms whereby we're trying to generate resources, the Office of Science can be involved in that from a neutral standpoint as opposed to a product orientation.

We in the Office of Science are in a position to receive information from all of these aspects that would be useful in developing research and science priorities; and to the extent that some of the money that is appropriated to the FDA, beyond what would be distributed to the centers for center-specific research needs, to the extent that the Office of Science would have a budget to support agency-wide research.

That may not get supported through other mechanisms within the centers; it would

be helpful if the Office of Science would have a small budget to support work also in the centers; not to hold that money, but to receive some and redistribute it to the centers to support work that might have come through the discipline teams or through other mechanisms of identifying high priority agency-wide research needs to supplement what will be supported through the individual centers.

Then to the extent that in the future we need to have research conducted, that the agency scientists are not prepared to handle themselves without major retooling, the possibility would be that we would also have extramural mechanisms whereby we could support researchers on specific projects outside the agency to develop the full complement of research needs that we would have.

Now most of the money to support that comes directly from these sources and is done in the centers; but the Office of Science could help redirect money to other high priorities that wouldn't be met otherwise.

DR. BLOUT: I'd like to ask the Board to comment on this sort of large group of subjects.

I know you've been thinking about it a lot, Bern, but I'd like to hear the Science Board comment if they feel it appropriate, on these large ---

Who wants to start? Marion?

DR. NESTLE: Sure, why not.

This is the statement from the new person in town. I'm impressed from reading the CBER report and from hearing this that the FDA has serious problems to deal with that include funding, and that's clearly a major one. But also it has to do with presentation of the agency in order to try to garner the funds that it needs.

I'm kind of in shock that the kinds of funding possibilities are being considered that you laid out. I think anything that puts FDA in an apparent conflict of interest is a slippery slope that you just don't want to get on, because it will destroy the integrity of

the agency and its ability to function.

The organizational issues, it seems to me, need to be addressed and need to be addressed very, very rapidly. And I see it as, from the standpoint of organizational structure, that there has to be a level of goal-setting and accountability that is readily apparent so that anybody who is looking at the agency can see instantly what the goals are and how well the agency is meeting its goals, and what it's doing to meet its goals.

We heard some of that; I like the goals, objectives, activities approach to it. I think it's a really good way of doing that.

I don't know enough about it to know how to go about starting on it, but 1'11 be most interested in hearing what it is. But I think this is a situation in which the agency needs to hold firm in a number of areas, and absolutely emphasize the importance of maintaining the integrity of the review and regulation process at every step of the way.

DR. BLOUT: Dr. Benet.

DR. BENET: I'll give a perspective of something that I have raised at previous meetings, and I think the best example of this is in CDER. That is, the strong interactive nature that the Center for Drugs has with scientific societies in its discipline, and the kinds of consensus-building issues that are presented at such meetings.

And then working together, lead to new regulation within CDER, and in fact some of the new regulations that have come out have come directly from those meetings.

But it seems to me also that there are research agendas that are beyond individual companies, and also beyond the FDA. I think it can serve as a focus -- it doesn't necessarily bring money directly into the agency, but it does solve some of the problems in science issues that the agency addresses.

I can see a particular scientific society in conjunction with all of its stakeholders including the FDA, suggest that this is a research project that we need to

address in terms of something that is important in the regulatory arena; and that that be the focus of generating the money and addressing the problem. It isn't necessarily money that comes in to FDA scientists because they're going to run that project, but they become part of this project through the, sort of the overall goal of this scientific society who generates, raises the money and generates, and in fact even controls the research, and the FDA like they are now, are coinvestigators in these projects.

But I think it allows us to get to some of the problems that we feel that we don't know how to address. And I can think from a CBER example, the ability to measure a certain biological or an adventitious agent or something like that, that says this is a problem for everybody. And therefore we put together an issue that the CBER scientists and the FDA scientists as well as the academic scientists and industry scientists under these -· the hierarchy of the scientific society

could have a potential of something we haven't done before; and yet works nicely as a model in terms of conceptual ideas, and I think could be addressed in terms of science ideas.

DR. BLOUT: Dr. Cuatrecasas.

DR. CUATRECASAS : I like those comments, and would just like to add again more broadly, that I think this is a good start, it's more than a start. I think this is the kind of thing you need to do to come to grips with the variety and complexity of problems that exist within the agency.

And it's not only in the area of funding, but there are issues, as you point out here, that go far beyond funding. It's not just finding more money. That's necessary but it's not sufficient.

I see here an attempt in a disciplined way to assess and to analyze and put on paper, which is different, particularly one page, something that begins to make some sense. It doesn't mean you've got all the solutions here, but you're beginning to really I think identify

some of the major issues, and you have to do that before you can achieve innovative solutions. So this is what's necessary.

These are very difficult times. Very difficult times, very complex times with respect to funding and availability of resources and the proliferation of scientific disciplines, and I think we need imaginative approaches .

So I would encourage you to continue with things even which may be ultimately for some reason unacceptable. Others may ultimately not be unacceptable, because you' ll find that there's a way to resolve that problem.

So I applaud what you're doing. It's not easy, and good luck.

DR . BLOUT: Dr. Langer?

DR . LANGER : I think what's said has been right; I think that what you're proposing is very, very important. The only issue is how to get there, and I think there have been some good suggestions.

DR. BLOUT : Any other comments?

Well, Bern, I know I speak for the Board in thanking you for getting us started in this way of thinking.

I've been told that -- it's in your book -- I've been told that I should announce that the next dates, planned dates for the Science Board meeting are October 21st and 22nd. I think it will only be a one day meeting, one of those two days. But would yOU hold the 21st and 22nd of October.

How does the Board feel about starting later than we have in the past; namely, 9:45 versus 8:30 or 9 o'clock? Is it satisfactory? It allows people on the East Coast to make it a one day trip rather than ---

Let me just summarize, before we ask for public comments, which are up next. Let me just summarize what I think the Science Board has done today; namely it has accepted -- first, it has accepted the report of the Subcommittee on Toxicology, and we'll look for subsequent reports.

Secondly, it has accepted the report on the Biomaterials Forum, and we'll put that on hold.

Thirdly, it has accepted the report of the Subcommittee for CBER review, subject to specific changes from science -- suggestions from Science Board members, and when those come in, we'll just send them out to everybody. It'll only be a few pages. We won't send the whole report, but we'll send them out to everybody before we take a final vote on acceptance.

Is that satisfactory to you, Les?

All right; now it's time for me to ask for any public comments. Anybody in the audience that wants to say something with respect to this meeting of the Science Board, please go to the microphone, identify yourself and your organization.

PUBLIC COMMENTS

MR. GOLDHAMMER: Alan Goldhammer, Executive Director, Technical Affairs, the Biotechnology Industry Organization.

The report a very good one; we just received it after the presentation. I would like to clarify, on page 4 in the second paragraph where you talk about the Pharma perception on the negotiations during PDUFA.

This was jointly negotiated with both of the industries; the biotech as well as the mainstream pharmaceutical industry. I think this is not quite fair to, even though we're not mentioned, but I would point out I don't think it's quite fair to characterize it that that was the tenor of the discussions.

Both organizations had a bottom line from our Board of Directors in terms of how much money we were prepared to contribute to the renegotiated PDUFA. And there were a variety of different program enhancements that we wanted as part of that negotiation, primarily oriented towards shortening drug development, which was something that was left out of the first round of discussions. We looked at just raw approval times in getting those down.

One of the things that came up probably midway during the discussions was the need for improvement of the computer system which would lead ultimately to full electronic submissions from IND all the way through to adverse event reporting. We said “Okay, that sounds good. We can see the benefits there. We can quantify those. What is the price tag?” That ended up being somewhere in the neighborhood of $12-15 million added on top of what we wanted for some of the other program enhancements .

The bottom line, in keeping with the price tag that the CEOS were willing to pay, we had to look for some cost savings. I think the reason that the CBER research unfortunately suffered, and I’ll address that in just a minute, was to try to bring this down to something that we could sell both boards of directors on; and hence the reason for this phaseout over the five period of time.

Our experience in terms of what we have heard from some of our CEOS and regulatory

affairs people is the research has been very beneficial in terms of dealing with clinical holds, either preventing a clinical hold or getting off of a clinical hold, addressing a number of difficult safety issues, particularly with regards to our membership we have companies doing xenotransplant, cell and gene therapy where there are real safety issues.

I think the agency is addressing those; we would like to see that continue. We're struggling I think with some of the proposals that you just saw with you as to how to achieve that. We would love to see it done out of appropriated funds, and we're going to work through the appropriations committee as we have over the last seven years to ensure that the agency is fully funded.

However, there are some political realities that may or may not make that difficult over the years to come, and we'll hope to try to work through some of those. We do have a board level committee that's going to be looking very closely at this report; we hope

to supply Dr. Benet as well as the Science Board with our input and take on it; but I think the bottom line is that we I think are all working to the common goal of increasing the agency's research resources, particularly in the areas that affect these new and emerging technologies.

DR. BENET: Thank you. I just want to make sure I understand: So you think that what I should have said was the perception of Pharma and Bios in the recent negotiations. In other words, I should have blamed both of you?

MR. GOLDHAMMER: Yes, you should have blamed both of us, because I'm sure that the Pharma people, when they see this, are going to say "Well, how come you left out Bio?" So I'm willing to be the scapegoat at least today, put myself on that stand. But I just wanted to also bring you up to what the realities we were facing were.

We had a bottom line of somewhere, about $115 million, I forget what it was, is what we could negotiate on. And it was very

difficult to try to work within that framework.

DR. BENET: Well, we certainly were aware -- I'm aware of it, and all we say there is, it's felt that the regulated industry not pay for CBER research. So I don't think that's incorrect. And we do address some of those issues, certainly the xenotransplanation issue the committee itself said "This is an area that needs to be beefed up. "

I just wanted to make sure what you thought I ought to correct.

MR. GOLDHAMMER: I think that's good; I think that the singlemost probably political thing that one could do -- although that's probably impractical -- would be to get FDA from out of the agricultural appropriations subcommittee and over to the HHS committee.

We're in a difficult position, because our board has agreed to support the doubling of NIH funds over the next kind of five or six years, and yet we're throwing -- throwing is maybe the wrong word -- we're putting this money towards basic research, but if we're

constricting the research effort at the agency, which ultimately could adversely affect product approvals , how can we derive the broader benefits of all the biomedical research? And that's a tough one.

DR . BENET : I think the committee certainly hopes that Bios and Pharma will express their concern that in fact in the PDUFA reauthorization and authorization, the idea was that we would not decrease the budget that came from the federal government for carrying out aspects of research; and that this would be additional money. And I think it's very clear that that has not happened.

MR . GOLDHAMMER : Yes.

DR . BENET : And I think again, when you look at the budget for CBER and compare to the years, it's very obvious that that has not happened.

MR . GOLDHAMMER : Well, there was also a very heavy line item in there for money that would come from the tobacco settlement which, as of this morning is still somewhere.

DR. BENET: Thank you.

DR. BLOUT: Mike, do I understand what you're saying is that there is a possibility of increased PDUFA funding? Or you're not saying that.

MR. GOLDHAMMER: No. The PDUFA -- well, on a yearly basis the funding can increase because there's an inflation indexer as well as a workload adjustor. In the budget request that FDA submitted to Congress this year, I believe they are asking for an increase -- 230 I believe it is, FTEs from the PDUFA program.

Primarily I think the baseline -- the negotiated baseline in the absence of the inflation and workload adjustor was $109 million for this fiscal year. Because of the inflation in workload, I think the agency will be collecting, I think it's over $109 million. For this fiscal year. Because of the inflation in workload, I think the agency will be collecting, I think it's over $130 million.

So there are extra personnel that will

be hired within FDA as a result of the PDUFA agreement, above what ought to have been because of the increased workload.

DR. BLOUT: What is your feeling that Pharma and Bios would be willing to support as far as science in the agency?

MR. GOLDHAMMER: We have a conference call on Thursday I'll have a better idea after that.

DR. BLOUT: Thank you.

Any other comments? Anybody just want to say something? Rosie.

MS. ELLISBERG: I'm Rosalie Ellisberg, Center for Devices, cochair of the FDA-wide junior science council, head of one of the discipline groups in Genetic Tox. I'm also President of the National Professional Scientific Society in this field.

My lab budget is $4,000 per year; that's all I have. And we are indeed all desperate in the fund raising area. I think, though, to talk about all these alternative sources of funding is really counterproductive.

Anybody who writes for grants knows that it's a full time job. And I think any of these other sources will divert us from our public health mission and purpose.

We seem to need outside help, though, to express to the world the fact that we don't have the critical funding that we need to function. And as far as comparing CBER and CDER goes, I think it's great that you've identified the really important public health issues going on a CBER. But I think there are similar but different issues in every center.

For instance, to say that the Center for Drugs has functioned without basically any research going on at all, very little, just begs the question: That could happen in CBER and maybe there would be contaminants in the vaccines and you wouldn't find out about it for a year or a decade, two decades.

In the Center for Drugs, I'm not in that Center, but I can think of a lot of issues that are critically important, such as drug interactions when more than one drug is taken

at a time. It's in no pharmaceutical company's interest to study this. It's in no pharmaceutical company's interest to really develop drugs for individual people with different genetic susceptibilities to drugs, because it would end up that you would be selling less of a given drug.

There are a lot of public health issues like this that FDA could address. In genetic toxicology, the test for cancer risk assessment, the simple tests done first, we're using assays that are 20 and 25 years old. And no one has the funding to develop new assays and to look into these.

This is another thing that FDA could do, it's an FDA-wide issue and Dr. Schwetz has tried very hard to institute FDA-wide issues.

We have no forum for this, and I do think that everybody would be more cooperative in FDA and among the Centers if we had appropriate funding. But since we have such little funding, we're fighting over every last dime and nobody wants to give up anything for

FDA-wide issues.

We're losing the public health mission here. I think the CDER report is a good step, and I hope, as Dr. Benet said, the Kern report didn't seem to have any effect on the law in Congress to beef up federal agency research funding, because FDA wasn't there. So somehow we're still not on their map. And I believe we should focus our efforts to getting on the map rather than talk about CRADAS and all these other things that are simply diverting us from the major purpose that we should have.

DR. BLOUT: Thank you, Rosie.

We happen to have two former drug company executives sitting around this table. Maybe one of them would like to comment.

(Laughter)

DR. SANDERS: 1'11 just respond in part, respectfully that it is in the company's interest to determine whether or not there are drug interactions, if there's some reasonable expectation that there might be. Not only from the point of view of protecting the patients,

because it's not good to have reactions to one's drugs, but also to seek competitive advantage over other drugs that might be used to treat the same conditions, to determine whether or not the other -- you might have an advantage in not having drug interactions.

It's an area which is I think far from zero or one; it depends on the circumstances and you've got to keep an open mind about it. But I don't disagree with you that the appropriate and most desirable way to solve the problems that you're facing funding research is to have appropriations; and that of course is a whole other subject of how you can get it at the Congress and make sure that you can make a case that says this is going to impact favorably the way that we do our job at the agency, and you know that lesson much better than I.

DR. BLOUT: Dr. MacGregor.

DR. NESTLE: Could I comment on what she just said before?

DR. BLOUT: Yes.

DR. NESTLE: I wanted to thank the previous speaker for raising issues, and it made me think that one thing that might be helpful in making the CBER report respond to Dr. Cuatrecasas' comment about needing to expand it a little bit wider would be to get from each of the divisions maybe two or three ideas of research projects that FDA could do that nobody else was doing, just to have a little catalog of the kinds of things that would make the FDA's research program much more understandable to the public, perhaps.

DR. CUATRECASAS: That was actually done with David Kern's committee --

DR. NESTLE: Sorry.

DR. CUATRECASAS: I'm not sure it's in the summary.

DR. BLOUT: No, it isn't.

DR. CUATRECASAS: Maybe you have to go to the appendices, and there were a lot of additional, supplemental things which in fact did that. And we talked to every center director, and they all made the case, they all

made a case about what kinds of research they were doing, what kind of research they could do, internally or externally; because a lot of it, a lot of the laboratory research that the other centers wanted to do could be done on contract; but they don't have funds for that, either.

So they made the case fairly strongly, and that was the reason that I -- I made this morning the comments that other centers have -- we just heard about that as well, and they affect public health equally.

DR. BLOUT: We've heard a lot about CDER and we happen to have somebody here who can speak to the question.

DR. MacGREGOR: I'm Jim MacGregor, I'm with CDER, FDA, the Office of Testing and Research. Actually, I wanted to comment on two aspects of the discussion.

The first is the strong distinction that was made in the committee report between the need for research in CBER and CDER, and it's been said before by others; but I just

want to say for the record that I consider it to be an untenable argument that science is less important for drug development than it is for biological. I think we all recognize that the advances in science have been enormous and they cross-cut all aspects of our agency, and it's a necessary aspect of our function to maintain knowledgeable scientific expertise that understand those new systems in order to do our job well.

The other thing I wanted to comment on was the discussion on collaborations . I'd actually like to raise a slightly different focus on it than has really been the emphasis of the discussion.

I personally believe that there are many broad, crosscutting scientific issues that need to be addressed that are equally important to the public, the industry and the FDA. In many of these cases the scope of resources exceeds that of even industry, and there are a number of examples of successful collaborations to identify these kinds of issues; and I think

it's more of an issue than just resources. It's also a matter of acceptance and the motivation to bring new science into the regulatory practice; because if industry and government are completely separated, each component has a very strong barrier against innovating if they're separated. And yet science demands innovation and evolution to use the new science for more efficient regulation.

And industry really cannot effectively come forward with a novel approach that the government doesn't know about, because it doesn't make product development sense to risk your product on something that you have no idea how the government is going to approach it.

So therefore if you accept that idea, the idea that you don't need science in the government and that you shouldn't talk to industry science I think is an untenable idea and we shouldn't lose sight of that fact.

In response to the concerns raised by Dr. Nestle about the danger and the impossibility of communicating with those that

you regulate, I think there are many precedents where that's been done successfully and is being done successfully, both in FDA and in other regulatory agencies.

Just to take a number of different kinds of examples, the Health Effects Institute is one example where an entire institute is built half by the EPA budget and half by the regulated automotive industries budget. And the entire purpose is to pool their resources to look at crosscutting issues like new fuels and particulate and ethanol additives to gasoline and how to treat them and so on.

And have a long history of successful approach to that sort of thing, and they're under exactly the same kinds of regulatory constraints as the FDA.

Then there was reference to the fact that you don't necessarily have to pass money between the agencies to pool your resources. And an example of that is the ongoing ILSI consortium on new models for carcinogenesis . There are about 40 laboratories working

together to look at these new transgenic models for carcinogenesis, evaluate how they work; and I would ask: Can the FDA afford not to be involved in that kind of science? I think the answer is no, that you cannot afford not to be involved in developing those kind of models and assessing their performance and so on. And yet most of the resources coming from industry in that case.

Yet it is our primary job to set the regulations, to define what the regulatory requirements are going to be. And 1'11 echo what Rosie said there; I mean, clearly I think we would all agree that it's necessary to have adequate appropriated funds to be able to fulfill that.

The other thing that I should point out that hasn't been mentioned today is right now there are some new collaborative efforts underway that involve CDER and CBER. The product quality research initiative and the collaboration for drug development improvement, which are both programs that are involving

industry, university, public and government sources are very real; they're public, they're ongoing, and I think they're going to contribute importantly to our mission.

DR. BLOUT: Thank you, Dr. MacGregor.

Does anybody want to respond?

DR. CUATRECASAS: Those were superb comments.

DR. MacGREGOR: Thank you.

DR. BENET: Jim, when you make the comments, there's no one that disagrees with science in the agency and its need in all aspects; and that's what you suggested maybe I was saying or the committee was saying.

The committee's point is the difference between laboratory research and virtual science. And as Bern gave in his talk, the agency has been moving more toward virtual science as opposed to laboratory science.

Now I know you meant to say this, but I'm just saying, the next time you say it, say it as laboratory science not just science, because --

DR. MacGREGOR: Let me just add that I just came to this agency to lead CDER'S laboratory effort.

DR. BENET: I know that, and I've known Jim for many years; I was on his wife's committee for her Ph.D., so I knew him back when he had brown hair, gray hair. And I think it's wonderful that you're there. And I don't oppose it; I believe it's important throughout the agency. I reflected what my committee's task was in terms of that. And I think you, Dr. Cuatrecasas and others, have pointed out that we need to be broader in this, and I don't object to that.

DR. BLOUT: You're saying there's a place for laboratory science in CDER as well as CBER.

DR. MacGREGOR: I didn't say there was a place; I said I think it's essential, just like it is in___.

DR. BLOUT: Thank you.

Any other comments? Anybody else? From inside or outside the agency.

Rosie, again?

MS. ELLISBERG: I think we're misinterpreting the virtual science center. I don't think it was juxtaposed against laboratory science. It was an all-encompassing term to link FDA science into one virtual science center, so we could work together. It's not one or the other; it's really -- we've all been in favor of lab science, more lab science. The virtual science center doesn't mean no lab science.

DR. BLOUT: Kathy? Dr. Zoon.

DR. ZOON: I just want to say, while I support working in the virtual framework, I think one can't forget that there has to be a direct interaction, either within a person or with people who do the review work. To have somebody off here asking questions and doing something and having review over here, and not having them interdigitate and supplement and foster and create the kind of environment that leads to the scientific knowledge base in accepting and promoting the science in the

review work that we do would be missing the point.

So I just want to make sure that while we're all supporting this, and I think it's wonderful, the cross-fertilization, we cannot forget the key importance of having that science directly linked to the regulatory process.

DR. BLOUT: Bern?

DR. SCHWETZ: I want to comment on the virtual aspect as well, because there are some places where it's more compelling than others.

For example, the recommendation to buy a multi mass spectrometer means that there's going to be a lot of other stuff that can't be bought if you buy that piece of equipment. And to the extent that we've got five or six of those sitting around the agency all being used part time, is not good management.

In that case, we've made an effort to bring the mass spec people together and compare notes on what capabilities do we have, where do we have it, how much of it is being used in a

given site, and if anybody else needs it, we ought to be using our mass spectrometers to the full extent that we have before we go out and buy additional ones.

So I think there are examples where the virtual approach doesn't make any difference, in particular, but there are some cases where it's extremely compelling that we look at the resources that we have before we just go out and buy additional expensive pieces of equipment making believe we have a lot of money.

DR. BLOUT: I think we're clarifying this word 'virtual'.

Anybody else?

If not, 1'11 ask the Board if they have any further comments, suggestions, before 1'11 ask for a motion to adjourn.

DR. CUATRECASAS: Elkan, just one other -- this morning, Michael Friedman talked about the issues and the topics which are being examined and are going to be prioritized and a part of the act; and I think he has to do this

by November.

One thing that was not mentioned, he only mentioned three areas, and he welcomed more suggestions. One that I have not heard and I think does need some attention is the whole question of chemistry and manufacturing standards. That's something again I can provide in a little bit more detail -- this would be across-the-board -- but increasingly complex and increasingly becoming rate-limiting in drug development.

It is not the clinical data development , nor usually the toxicology that is rate limiting, generally, with few exceptions. I'm seeing more and more the development process, the discovery process being held up by issues that relate to chemistry and manufacturing. They definitely need to be examined, and I don't know how much of that is happening.

DR . BLOUT : Less and less; and those of us who have been involved product development at one time in our lives realize

the importance of that, and the very expensive nature of that kind of activity.

Good point. Let's put that in our thinking.

Any other comments?

DR. MacGREGOR: Well, just with regard to the last comment, I might point out that this product quality research initiative that I just referred to is directed specifically at those kinds of issues; the quality issues, the chemistry, quality manufacturing issues and the amount of regulations that are necessary during scaleup process; all these sorts of issues.

So there is recognition of that, and this is one of those things that we're trying to tackle through this joint industry-government-public collaborative approach.

DR. CUATRECASAS: Thank you.

DR. BLOUT: Good point. Thank you, Jim.

All right; anybody else?

If not, do I have a motion to adjourn?

[Moved.]

DR. BLOUT: So be it. We'll see you all in October if not before. Thank you.

[Whereupon at 2:29 p.m., the meeting concluded. 1